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(Continued from the January issue)

BLOOD VOLUME IN PREGNANCY*

A Critical Review and Preliminary Report of Results With a New Technique

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FROM time to time and for various reasons investigators have interested themselves in the question of what happens to the volume of the blood during pregnancy. With the passage of years new and presumably better techniques for the determination of blood volume have become available and have been applied to the problem. Thus, as might be expected, no two studies have been carried out by exactly the same technique, and each author, in turn, has questioned the validity of previously reported results. Despite the fairly general acceptance of the notion that there is a real increase in volume of plasma and red cells‡ during pregnancy, there is no agreement as to the precise magnitude of this increase at the various stages of gestation or the rapidity with which the volumes return to normal in the postpartum period. The possibility that the dye-dilution method for plasma volume might be subject to a sizable error owing to dye which passes to the fetal circulation, or which is merely trapped in the placenta, has been considered, but apparently never very extensively. The advent of still another modification of the dye-dilution method, designed to eliminate some of the errors inherent in earlier techniques, suggested to us the desirability of reopening the question of blood volume in pregnancy to see whether divergent viewpoints now recorded in the literature might be clarified.

Soon after the development in 1915 of the Keith-Rowntree method[1] for plasma volume, using vital red, it was applied to pregnant women by Miller,

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‡Throughout this paper PV = plasma volume, TBV = total blood volume, and RCV = red cell volume.

Keith, and Rowntree.[2] But their supply of dye was cut off by World War I, and they were able to make determinations on only thirteen patients anywhere from two to sixty-one days before labor, and on eleven of these women from one to eleven days post partum. In each instance there was a post-partum decrease in TBV, but not invariably when calculated per kilogram of body weight. Their data show enormous variations in TBV both before delivery (range, 3 to 7 liters) and afterwards (2.5 to 5 liters). The more recent experience with the Keith-Rowntree method in 100 attempted observations at the Boston Lying-in Hospital[3] makes one question the validity of Miller's figures.

In 1934, Dieckmann and Wegner[4] published the results of a much more extensive blood volume study. They employed the method of Keith and Rowntree, but substituted Congo red for vital red because some of their subjects were seriously discolored by vital red. Their conclusions were: (1) TBV and PV begin to increase in the first trimester, with gains of 16 and 18 per cent, respectively, "by the thirteenth week;"* (2) the *average* increase at term is 23 per cent for TBV and 25 per cent for PV; (3) by eight weeks post partum the average decrease is 16 per cent for both TBV and PV. These values were calculated by a peculiar mathematical manipulation which involved the assumption that the first antepartum value obtained for any subject represented the true base line for that individual. All subsequent values were divided by this initial figure, the quotient being multiplied by 100 to compute percentage of change. Similarly, the post partum changes were computed by using the value obtained at term as a divisor. Thus, the 23 per cent increase in TBV represented the *average* increase for fourteen patients, but it should be pointed out that two subjects actually exhibited a *decrease,* and two showed "no change" (a variation of less than 5 per cent). Their table in which post-partum changes are summarized shows an *average decrease* in the early puerperium of 13.5 per cent, yet it appears from the detailed data for the various subjects that seven of thirteen women had a *greater* TBV one or two weeks after delivery than they did at term. Because of these inconsistencies we computed standard errors for Dieckmann and Wegner's data, and compared differences between the means of their values at various stages of gestation. The results are shown in Table I. The

TABLE I. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN TOTAL BLOOD VOLUMES IN C.C. AT VARIOUS TIMES ANTE PARTUM AND POST PARTUM, CALCULATED FROM DATA OF DIECKMANN AND WEGNER

GROUPS	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R*	P	SIGNIFICANT DIFFERENCE
12-20 wks. : 36-40 wks.	800	390	2.05	0.0404	?
12-20 wks. : 2 wks. pp.	655	387	1.69	0.0910	No
12-20 wks. : 8 wks. pp.	102	465	0.21	0.8337	No
36-40-wks. : 2 wks. pp.	145	325	0.45	0.6527	No
36-40 wks. : 8 wks. pp.	902	415	2.17	0.0300	?
2 wks. pp. : 8 wks. pp.	757	412	1.83	0.0672	No

*R is the ratio of difference to its standard error.

†This statement apparently is in error and it seems likely that the authors meant to say "by the thirtieth week," since their Table 8 shows average increases for the period 26-35 weeks amounting to 15.8 per cent for TBV and 18.2 per cent for PV.

thirteen subjects in their "Series A," studied at 9 to 20 weeks ante partum, at term (36 to 40 weeks), 11 to 14 days post partum, and eight weeks post partum showed mean values which were not significantly different at any of these times, unless one chooses to claim that an R value of just over 2.0 denotes a difference of real significance. Looking at the data in this light would suggest either that blood volume does not change significantly during pregnancy and the puerperium, or that the method employed in the study was unreliable.

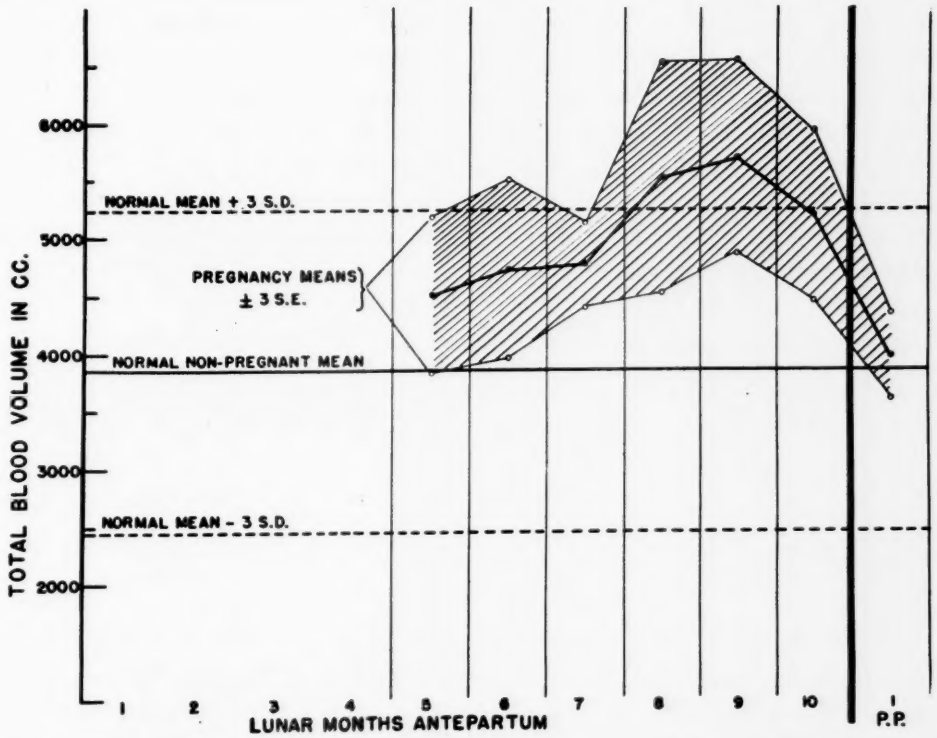

Fig. 1.—Curve of mean total blood volume during pregnancy, from data and chart of Thomson and associates, redrawn to indicate limits of mean ± 3 standard errors (cross-hatched area). Note that the mean value for the ninth month falls well within the range of mean ± 3 standard error for the tenth month, indicating that the difference is not significant. Similarly, the difference between mean values at five and ten months is of questionable significance.

The next careful study of blood volume in normal pregnant women was reported by Thomson, Hirsheimer, Gibson, and Evans in 1938.[3] Using the azo dye Evans blue (T-1824) and the method of Gregersen, Gibson, and Stead,[5] as modified for clinical use,[6] they made determinations on fourteen women at various times throughout pregnancy and the puerperium, and compared the results with values for a group of twenty-eight normal nonpregnant women included in the study of Gibson and Evans.[7] Their values for pregnant women were grouped according to lunar month (from five to ten, inclusive) and averages were determined for each group. Arranged in this way, the data indicated for PV an increase of 65 per cent above the average nonpregnant value, this peak being reached in the ninth lunar month rather than at term. During the tenth lunar month the increase amounted only to 52 per cent, and by the end of the second week post partum the normal nonpregnant level was reached. Similar curves were shown for TBV and RCV, with maximum increases in the

ninth lunar month amounting to *46 per cent* and 17 per cent, respectively. These investigators concluded that there is a progressive increase in PV and TBV beginning early in pregnancy, reaching a maximum in the ninth lunar month, with a "definite decrease" beginning during the tenth month and a rapid decline to normal values by the end of the second postpartum week.

Closer scrutiny of Thomson's[3] original data reveals that the maximum values shown at the ninth lunar month represent averages of determinations made on only eight women, and that some of the other average values are based on as few as four or five individual determinations. When standard errors are computed for the various means, and significance of differences determined, it is seen that the peak value for TBV is *not* significantly different from the somewhat lower average value found in the tenth month. Indeed, there is considerable doubt that the mean value shown for the fifth ante-partum month is really significantly different from the value at term. On the other hand, there appears to be no question as to the reality of the difference between the nonpregnant value for TBV and that found at term in the pregnant women (Table II, Fig. 1).

TABLE II. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN TOTAL BLOOD VOLUMES IN C.C. FOR NONPREGNANT CONTROLS AND PREGNANT WOMEN AT VARIOUS STAGES OF GESTATION, CALCULATED FROM DATA OF THOMSON, HIRSHEIMER, GIBSON AND EVANS

GROUPS	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R	P	SIGNIFICANT DIFFERENCE
5 mos. ante partum : term	710	339	2.10	0.0357	?
9 mos. ante partum : term	508	371	1.37	0.1700	No
5 mos. ante partum : 9 mos.	1218	358	3.40	0.0007	Yes
Controls : term pregnant	1365	265	5.15	0.0001	Yes

Very recently there appeared the study by Roscoe and Donaldson[8] in Edinburgh. This paper was published after our work was started, but since it did little to clarify the issues, we thought it worth while to proceed as planned. Roscoe and Donaldson used the technique for Evans blue which was described by Davis,[9] and which involves taking only a single sample of dyed plasma ten minutes after injection of the solution of Evans blue. Their values for blood volume were expressed as milliliter per square meter of surface area, although they pointed out that the formula used to compute area probably did not give the actual surface area in a pregnant woman. The fallacy of assuming in pregnancy a correlation between blood volume and weight of subject (surface area being related to weight) was pointed out by previous writers.[3, 4] Twenty women at three different stages of pregnancy were used as subjects, and twenty normal nonpregnant women served as controls. Taken individually, the results were somewhat erratic, in that some patients exhibited a drop in volume between the twelfth and twenty-fourth week of pregnancy, while others showed a drop between the twenty-fourth and thirty-sixth weeks. But the mean values for the three periods demonstrated a steady upward trend for TBV from 4,300 c.c. at twelve weeks to 5,400 c.c. at thirty-six weeks, or an increase of about *25 per cent* in absolute volume. Expressed in terms of surface area the increase

amounted to *18 per cent.* In many cases the blood volume at the end of pregnancy was not outside the range of values found in nonpregnant women and the blood volume became more variable as pregnancy advanced. There was no significant difference between the mean blood volume at twelve weeks of gestation and the mean volume of the nonpregnant group, nor between the mean values at twenty-four and thirty-six weeks. However, the mean value at thirty-six weeks was significantly higher than that at twelve weeks (Table III).

TABLE III. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN TOTAL BLOOD VOLUMES IN C.C. FOR NONPREGNANT CONTROLS AND PREGNANT WOMEN AT VARIOUS STAGES OF GESTATION, CALCULATED FROM DATA OF ROSCOE AND DONALDSON

GROUPS	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R	P	SIGNIFICANT DIFFERENCE
Controls : 12 wks. ap.	50	158	0.32	0.7490	No
Controls : 24 wks. ap.	550	199	2.76	0.0058	Probably
Controls. : 36 wks. ap.	1050	259	4.05	0.0001	Yes
12 wks. ap. : 24 wks.	600	175	3.42	0.0006	Yes
12 wks. ap. : 36 wks.	1100	205	5.35	0.0001	Yes
24 wks. ap. : 36 wks.	500	236	2.12	0.0340	No

Method

In recent years many techniques employing the blue azo dye, Evans blue (T-1824), for determination of plasma volume have been described, and the inexperienced worker may be at a loss to know which method to follow.[10] We have combined the most desirable features from a considerable number of techniques, hoping to achieve the greatest possible accuracy. In general, we have combined the basic features of the original method of Gibson and Evans[6] (adapted to the Evelyn[11] colorimeter by Gibson and Evelyn[12]) with the chromatographic extraction of Morris.[13] The chromatographic technique of Morris has been perfected in our hospital by Hecht and Greenberg,[14] and we are indebted to Dr. Hans Hecht for instruction in the use of this method which insures virtually complete recovery of Evans blue from plasma.

Briefly we proceed as follows: A previously standardized 0.35 per cent solution of Evans blue in distilled water is injected into an antecubital vein in 9 to 10 c.c. quantities, the exact amount being determined by weighing syringe, needle, and solution before and after injection according to the method of Price and Longmire.[15] A torsion balance with a capacity of 120 Gm., accurate to ± 5 mg., is used for weighing the dye solution. At intervals of ten to fifteen minutes after the injection four to five samples of blood are removed through a 20-gauge needle from another antecubital vein, without stasis, or preferably from a femoral vein through an 18-gauge spinal-type needle which remains in situ until all samples have been drawn. The blood is collected in oxalated tubes and plasma removed after centrifugation at 3,000 r.p.m. for thirty minutes. Hematocrit values are obtained on the first and last samples. One cubic centimeter of plasma from each sample is mixed with 0.2 c.c. of 0.1 N sodium hydroxide solution, and 1 c.c. of this mixture is adsorbed on a column containing a mixture of aluminum oxide and magnesium oxide. The column is washed first with distilled water and then with an acetic acid-alcohol mixture to remove plasma proteins and pigments. Finally the Evans blue is eluted from the adsorbent with a mixture of hydrochloric acid and absolute alcohol, and the concentration of dye in the eluate is determined colorimetrically. Using the concentrations found at various times, a disappearance curve is plotted on semilogarithmic paper and is extrapolated to zero time (i.e., time of injection). The concen-

tration of dye at zero time is used in the usual formula[7, 12, 15] to compute plasma volume, and from PV the TBV is found from the equation:

$$\text{Total blood volume} = \frac{\text{Plasma volume} \times 100}{100 - \text{hematocrit}}$$

When determinations are repeated in the same individual an initial so-called "dyed dye-free" sample of blood is obtained before injection of further dye, and the extrapolated value for concentration is corrected by subtracting the L value of the "dyed dye-free" sample. The method obviously is tedious and time-consuming, requiring from three and one-half to four hours to complete all of the steps in a single determination. We do not recommend it for routine clinical use.

Material

Twenty women at term (thirty-eight to forty weeks) with normal pregnancies were observed either before the onset of labor or early in the first stage. Repeat determinations were done on each of these women on the seventh postpartum day. Seven other women were given varying amounts of dye, while in labor or before cesarean section, and umbilical cord blood from these was examined for the presence of dye. Ten normal nonpregnant women from the gynecologic ward were used as control subjects.

Results

Controls.—In ten normal women of childbearing age TBV ranged from 3,070 to 4,500 c.c., and the mean was 3,974 ± 140 c.c. The range for PV was from 1,815 to 2,640 c.c., mean 2,326 ± 78 cubic centimeters. These values may

TABLE IV. THE PLASMA, TOTAL BLOOD, AND RED CELL VOLUMES FOR TWENTY NORMAL WOMEN IMMEDIATELY BEFORE AND SEVEN DAYS AFTER DELIVERY

CASE	AGE	PARA	WEIGHT AT TERM (POUNDS)	WEIGHT SEVENTH POST PARTUM DAY (POUNDS)	HEIGHT IN INCHES	AT TERM			SEVENTH POSTPARTUM DAY		
						PLASMA VOLUME IN C.C.	TOTAL BLOOD VOLUME IN C.C.	RED CELL VOLUME IN C.C.	PLASMA VOLUME IN C.C.	TOTAL BLOOD VOLUME IN C.C.	RED CELL VOLUME IN C.C.
1	23	iii	158	145	65	5855	8245	2390	3370	5000	1630
2	25	v	203	175	65	4970	7895	2925	3285	5650	2365
3	19	i	188	158	65½	4225	7260	3035	3160	4930	1770
4	29	0	176	157	66	3760	5960	2200	3320	5410	2090
5	30	iv	161	143	60½	3475	5860	2385	2570	4350	1780
6	19	0	136	115	62	3420	5440	2020	2890	5100	2210
7	23	iii	160	141	65	3385	5390	2005	2950	5000	2050
8	40	xv	153	132	65	3320	5090	1770	2850	4500	1650
9	28	vii	139	122	60	3295	5300	2005	2560	4370	1810
10	18	i	138	123	61	3205	5030	1825	2395	3720	1325
11	19	0	110	100	64½	3140	5050	1910	1755	3195	1440
12	22	i	171	155	61	2920	5025	2105	2255	3680	1425
13	19	0	130	114	62½	2875	4710	1835	2295	3910	1615
14	19	i	110	101	60	2850	4800	1950	2185	3840	1655
15	20	0	130	112	62	2775	4270	1495	1915	2910	995
16	22	i	144	132	60½	2670	4110	1440	2310	3870	1560
17	20	i	115	102	61½	2515	4170	1655	2195	3765	1570
18	20	0	119	100	61	2330	3695	1365	2280	3630	1350
19	18	0	127	115	62½	2300	3910	1610	2290	3875	1585
20	17	0	159	138	64	2250	3875	1625	1755	3025	1270

be compared with those of Thomson and associates[3] whose 28 normal women (From Gibson and Evans' larger series[7]) had a range of TBV from 3,030 to 4,870 c.c., mean 3,845 ± 89 cubic centimeters. Their mean value for PV was 2,324 ± 54 c.c., which is remarkably similar to our average value. RCV for our controls varied from 1,255 to 1,970 c.c., with a mean value of 1,649 ± 75 cubic centimeters. It seems fair to conclude that our method produces results which are similar in magnitude to the standards for normal women established by Gibson and Evans.

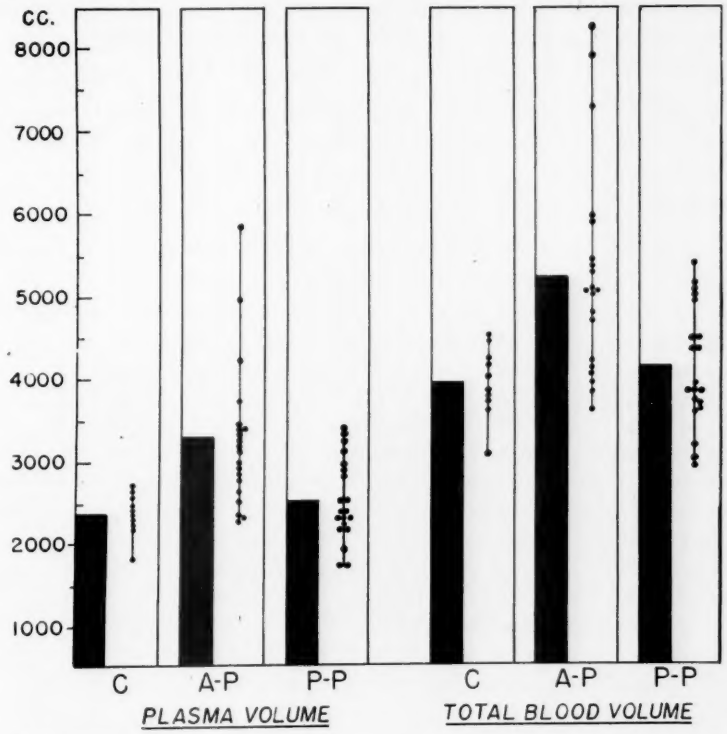

Fig. 2.—Plasma volume and total blood volume in control subjects (C), in normal women at term (A-P), and on the seventh postpartum day (P-P). The solid columns indicate the mean values, the perpendicular lines show the ranges, and the dots on these lines are individual values.

Pregnant Women at Term.—Twenty women (Table IV and Fig. 2) in this category had their blood volumes determined within two weeks of the delivery of a full-term infant. Twelve were studied on the day of delivery, the others at various times in the thirty-ninth and fortieth weeks of gestation. Plasma volumes varied from 2,250 to 5,855 c.c., the mean being 3,277 ± 205 c.c. The lowest value for TBV was 3,695 c.c., and the highest 8,245 c.c., with a mean of 5,254 ± 296 cubic centimeters. Red cell volumes ranged from 1,365 c.c. to 3,035 c.c. and the mean value was 1,978 ± 102 cubic centimeters. When compared with the nonpregnant series, PV and TBV were significantly greater in the pregnant women, while the significance of the increase in RCV was open to some question (Table V). At term the average increase in PV amounted to 41 per cent of the control value, and the increase in TBV to 32 per cent. The rise in RCV was only 20 per cent.

Postpartum Patients.—Seven days after delivery the same twenty women had plasma volumes (Table IV, Fig. 2) varying from 1,755 to 3,370 c.c., with a mean value of 2,530 ± 114 cubic centimeters. Correspondingly, TBV varied from 2,910 to 5,650 c.c., with a mean of 4,187 ± 179 cubic centimeters. The

TABLE V. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN VALUES FOR PLASMA, TOTAL BLOOD, AND RED CELL VOLUMES IN CONTROL SUBJECTS, ANTEPARTUM PATIENTS, AND POSTPARTUM PATIENTS

GROUPS	PER CENT INCREASE OR DECREASE	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	R	P	SIGNIFICANT DIFFERENCE
Plasma volume—						
Controls : term pts.	40.8	951	219	4.34	0.0001	Yes
Term pts. : pp. pts.	22.8	747	234	3.19	0.0014	Yes
Controls : pp. pts.		204	138	1.48	0.1389	No
Total blood volume—						
Controls : term pts.	32.2	1280	327	3.91	0.0011	Yes
Term pts. : pp. pts.	20.3	1067	344	3.10	0.0019	Yes
Controls : pp. pts.		213	227	0.94	0.3472	No
Red cell volume—						
Controls : term pts.	19.9	329	126	2.61	0.0091	Probably
Term pts. : pp. pts.	16.2	321	127	2.53	0.0114	Probably
Controls : pp. pts.		8	107	0.07	0.9442	No

average value for RCV was 1,657 ± 76 cubic centimeters. In each instance the postpartum values for PV and TBV were lower than the antepartum values, but in two patients (Cases 18 and 19) the decreases were scarcely worthy of mention. The average drop in PV amounted to about 23 per cent of the predelivery value, and for TBV the loss was 20 per cent. The differences between antepartum and postpartum mean values were statistically significant, with the possible exception of that for red cell volume (Table V). The difference of 204 c.c. between average PV in postpartum and nonpregnant women is *not* statistically significant, nor is the difference between postpartum TBV and the corresponding control value for nonpregnant subjects. Thus, it might be fair to say that in the main the postpartum average values have returned to the control levels by the end of one week.

Placental Transmission of Dye.—Seven women were given Evans blue in amounts ranging from 10 to 100 c.c. of a 0.35 per cent solution (i.e., from 35 to 350 mg. of dye) anywhere from twenty-five minutes to forty-eight hours before delivery of the placenta. In each case placental or fetal blood was obtained at delivery and examined by the chromatographic procedure described above. In only one instance was the colorimeter reading of sufficient magnitude to suggest the possible presence of an appreciable amount of dye, but in this sample (forty-eight hours after dye injection) no dye could be identified in a Beckman spectrophotometer. In the case of the patient who received 100 c.c. of dye solution, the maternal surface of the placenta was remarkably blue (three and one-half hours after injection), and the patient's lochial discharge had a bluish tinge for several days. Thomson and co-workers[3] reported their inability to find dye in cord blood serum or amniotic fluid after giving 30 mg. of dye to three women in labor, nor could they detect any dye in placentas prepared by a special technique. They assumed, therefore, that dye did not disappear from the maternal blood stream by passing to the fetus. While our observations do not confirm this assumption beyond question, they at least suggest that, at most, only very minute amounts of dye are transferred across the placental barrier within the first few hours after injection. It is unlikely that the value for plasma volume is greatly magnified by loss of dye to the fetal circulation. On the other hand, our observation in the patient receiving the very large amount of dye (350 mg.) suggests the possibility that dye may be trapped in the placenta and thus removed from the maternal circulation. Selective localization of Evans blue in the placenta of rats has been reported by Brunschwig and

co-workers.[16] We propose to study this phase of the problem more fully when suitable Negro subjects become available. In white women the massive doses of dye produce an undesirable bluish discoloration of the skin.

Comment

This study indicates that in all likelihood there is a significant increase in plasma volume and in total blood volume during the course of normal pregnancy. In our series the average increase at term in PV was about 41 per cent, and in TBV approximately 32 per cent. These values are higher than those suggested by Dieckmann and Wegner,[4] but for TBV the result is exceedingly close to the figure reported by Thomson and associates[3] for women at term. Their increase for TBV, strangely enough, was identical with ours, but their increase in PV was about 10 per cent greater. However, Thomson's values at the ninth lunar month were considerably above those at term, particularly PV which seemed to have increased 65 per cent over the normal at that point. The statistical insecurity of these latter values has already been discussed in reviewing the literature.

Despite the apparent increase in volume where group averages are considered, it should be pointed out that the range of PV and TBV in pregnancy is enormous. Presumably there is a good deal of overlapping of the normal distribution curves for blood volume in pregnant and non-pregnant subjects, although there is no question about the significance of the difference between mean values for these groups (Table V). But when it comes to the individual patient, one is not justified in assuming that an increase in PV amounting to 40 or 45 per cent will have occurred by the fortieth week of gestation, or that a decrease of 23 per cent will be manifest within a week after delivery.

If the question of changing blood volume in pregnancy is to be further clarified and reliable standards established, a great many more determinations must be made at all stages of gestation, of parturition, and in the puerperium. We feel that the method employed in this study is not suitable for routine survey of a very large number of patients because it is far too time consuming. Recently we have employed the single ten-minute sample method advocated by Gregersen and others,[10, 17, 18, 19] comparing this with the extrapolation of a disappearance curve. The values for PV obtained from a single sample are always a little greater than those found by using an extrapolated "L" value, but the increase amounts to only 3 or 4 per cent. If one is interested only in trends rather than absolute values the shorter procedure should be perfectly adequate, providing proper precautions are taken in obtaining and processing the single sample. We have assayed three different fractions of the ten-minute sample on separate chromatographic columns in order to detect errors in technique. As Gibson and others[20] have pointed out, there is no agreement that dye-plasma techniques measure with accuracy the TBV or circulating RCV, because the assumption that the hematocrit of blood flowing through the entire vascular bed is a constant at all times is probably erroneous. Using radioactive iron, they found RCV to be about 15 per cent less than when measured by the dye method. It is hoped that the newer radioactive iron techniques[21, 22] may ultimately be

applied to the study of blood volumes in pregnancy, but unfortunately the materials and apparatus required are rather elaborate and costly.

The authors of previous papers on blood volume in pregnancy have speculated freely on the cause or causes of the apparent increase in volume. Our study has not aided in the solution of this problem, nor has any significant new development along this line turned up in the past nine or ten years. The recent finding of Furth and Sobel[23] that granulosa cell tumors in mice were associated with hypervolemia revives the suggestion that increased estrogen levels are in some way concerned with elevation of the blood volume.

Summary and Conclusions

A chromatographic technique for extraction of Evans blue from plasma has been used to determine plasma volume, and from this value the total blood volume is calculated by use of the hematocrit. Determinations were made on twenty normally pregnant women at term and on the same women seven days after delivery. A control group of ten normal nonpregnant women was used to check the results with our technique against previously determined standards for normal females.

At term the average value for plasma volume was about 40 per cent greater than PV in the control series and total blood volume was 32 per cent greater. While red cell volume appeared to rise about 20 per cent, the significance of this change was not so striking as in the case of PV and TBV.

Within a week after delivery, blood volume had returned virtually to nonpregnant levels.

Individual variation in blood volume during pregnancy is enormous. Standard deviations are relatively much greater for pregnant subjects than for either the controls or postpartum patients.

A few observations indicate that the dye-dilution method is not invalidated by transfer of dye across the placental barrier, but the question of dye being trapped at the placental site is still unsettled.

Data from several previous publications have been subjected to statistical analysis and certain unwarranted conclusions previously made have been critically reviewed.

It seems unlikely that anything yet published, including this report, has given a thoroughly reliable picture of what happens to blood volume in pregnancy. A great many more determinations should be made and the validity of dye techniques must be ascertained by the newer radioactive iron procedures for red cell volume.

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Discussion

DR. WILLARD ALLEN, St. Louis, Mo.—Dr. McLennan's paper brings a surprising and pleasing note to the meetings. Here is a paper by an obstetrician and gynecologist who utilizes one of the newest tools of the chemical laboratory as an aid for the study of an old problem. I refer to chromatographic absorption. He then subjects his final figures to rigid statistical analysis. The figures he has obtained leave no room for any doubt concerning the presence of a marked decrease in blood volume in the first week after delivery. Each one of twenty patients studied showed a lower blood plasma volume on the seventh postpartum day than they did at term. This obviously is significant. I do not have a sufficiently good grasp of the levels of significance of the standard errors to elaborate on this point. I need only mention, however, that where the observations are consistent for 20 successive observations, the probability of the result being due to chance is extremely remote.

I have taken the liberty of doing some additional calculations from his data, just to enable me to make some remarks on the role which the sex hormones probably play in the metabolic changes occurring in pregnancy. Dr. McLennan is fully aware of the significance of his observations, but I think in his desire to confine himself only to the facts, he has omitted any remarks about the possible origins of these changes in blood volume which he has observed. Being only a discusser, I can be forgiven perhaps for indulging in some speculation.

The average loss of weight in his twenty patients was 17 pounds. If we allocate 10 pounds of this to the baby, placenta, and amniotic fluid, there still remains 7 pounds. This is only 5 per cent of the weight of the mother (minus the 10 pounds assigned to the baby, placenta, etc.). Now recall that the decrease in blood volume is approximately 20 per cent. This shows that the decrease in blood volume is not explained simply by the decrease in weight of the patient. This simple calculation only serves to emphasize the magnitude of the decrease and to provide grounds for speculation on the cause.

It seems to me quite clear that the metabolic change occurring during pregnancy can be attributed to the presence in the maternal organism of large amounts of estrogens and progesterone. Also, there is ample evidence that these sex hormones come from some source other than the ovaries in the woman. The evidence all points to the placenta as the extragonadal source. The delivery of the placenta suddenly deprives the woman of her sex hormones. She is, in fact, relatively more deficient in hormones four or five days post partum than at any other time in her life. It is because of the deficiency that she lactates. It seems easy to assume that the metabolic changes such as the loss in weight, the increased excretion of nitrogen, the decrease in blood volume—to mention only three—are brought about by the deficiency of sex hormones induced by the delivery of the baby and placenta. The argument would, of course, be less fanciful if there were some shreds of evidence on the positive side. Fortunately there are. In the monkey the fetus has been removed leaving the placenta intact. Such animals, deprived of their babies but retaining functioning placentas, continue to gain in weight. The placenta is delivered at term, whereupon the monkey returns to her prepregnant weight.

Finally, as still further evidence that the metabolic changes surrounding delivery are tied up with a loss of placenta, we have made studies on a case of abdominal pregnancy in which a living fetus weighing 4,000 Gm. was removed, the placenta being retained. Our index of change in metabolism was the change in the urinary excretion of sodium pregnandiol glucuronidate and nitrogen. For about three weeks following delivery there was a gradual decrease in the excretion of sodium pregnandiol glucuronidate, but with no change in the excretion of nitrogen. Then there was an abrupt fall in the excretion of sodium pregnandiol glucuronidate, indicative of cessation of production of progesterone. This deprivation of the body of progesterone (and probably estrogen) was followed by an increase in the excretion of nitrogen.

DR. GORDON DOUGLAS, New York City.—Dr. McLennan has reviewed the literature and applied critical statistical methods in an attempt to evaluate accurately the recorded data of this interesting subject. One is immediately impressed with the relatively small number of cases in any given series. This fact alone introduces difficulties in evaluating the data from a statistical point of view. The author deserves great credit for working on such a difficult problem. For each test it is necessary to have a willing "normal" patient who can hardly escape making the observation that she is the subject of investigation. Long, exacting, and tedious work in the laboratory must follow when a patient consents to subject herself to such investigation. It is very easy to say that a larger series of patients with repeated studies, conducted at various periods of gestation and the puerperium, would settle the problem. When individual variations in blood volume are so great, the importance of making repeated observations on the same patient becomes even more important. Perhaps newer techniques that Dr. McLennan has referred to will facilitate such investigation.

From a clinical point of view I think it particularly important that these studies be carried out to give us more exact information during the last four weeks of pregnancy and during the early puerperium. It is during this time that water retention followed by diuresis is such a frequently observed clinical phenomenon. Just what happens to the blood volume during this time has a very definite bearing on the management of pregnancy complicated by heart disease, toxemia, and other complications that are frequently encountered at this time.

The tremendous individual variations in blood volume recorded by the author confirms previously recorded figures. At the present time there is no entirely satisfactory explanation for the phenomenon. Dr. McLennan has pointed out the inaccuracies of the statistical data of Thompson and the fact that that claim cannot be substantiated. Additional studies may open a new horizon for the study of these poorly understood changes.

DR. McLENNAN (Closing).—I am grateful to Dr. Allen for speculating on some of the reasons for these changes in blood volume. Obviously, time interfered with any mention of that on my part. That aspect of the subject, of course, could take up the entire space of a dissertation. And I am grateful to Dr. Douglas for pointing out the difficulties that arise in doing research of this kind. Patients begin to shy away from needles when they discover that a simple thing like blood volume requires six or eight venapunctures today and a repetition of that a week or so later. In order to overcome that hesitancy, we have resorted to the use of an indwelling femoral vein needle.

Dr. Douglas commented on the clinical manifestations, particularly the relation between the blood volume and the changes that occur in the cardiac patient. That is the one clinical field where blood volume studies have been most frequently employed; that is, the changes in blood volume have been pointed to as one reason perhaps for not terminating pregnancy three or four weeks before term, in view of the fact that many people have thought that blood volume decreases terminally, and therefore the cardiac condition improves, and there should not be any urgent reason for premature delivery. But this thesis has not been clearly proved.

I had no opportunity to mention that the Evans blue dye may escape in part to the placenta and get into the fetal circulation. A few people have tried to find out whether the dye can be recovered from the infant's blood. We tried to do this, and, while the data available are not thoroughly convincing, we suspect that very small amounts of this dye may be transferred across the placental site. Whether larger amounts of dye are actually trapped *at* the placental site is a question which no one has as yet properly answered.

MALIGNANT TUMORS OF THE OVARY*

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THIS study consists of a brief review of all of the cases of malignant disease of the ovary that were treated in the Division of Gynecology of the Department of Obstetrics and Gynecology in the Jefferson Medical College Hospital between Oct. 1, 1921, and Oct. 1, 1946. The clinical and pathologic records have been reviewed, and all histologic slides have been re-examined in collaboration with Dr. Peter A. Herbut. The original pathologic diagnoses were made by Baxter L. Crawford, M.D., (deceased), C. J. Buchner, M.D., and Jacob Hoffman, M.D.

Material

One hundred nineteen cases were available for study. Twelve of these, all with advanced carcinoma, have been discarded because the microscopic slides were not available or the diagnosis was in doubt. Of the remaining 107 cases, eighty-four were primary carcinomas of the ovary, seven were large carcinomatous tumors of the ovary secondary to uterine cancer, two were adenocarcinomas occurring in teratomata, ten were granulosa cell tumors, one was a Krunkenberg tumor, two were dysgerminomas, and one was a Brenner tumor. Although our interest centers in the adenocarcinomas, the record of our end results in ovarian malignancy would be incomplete if we were to exclude the other types mentioned from our study. They will be reviewed separately.

The ages of the eighty-four patients with adenocarcinoma may be recorded in decades as follows:

Years	*Patients*
Under 20	1
20 to 29	8
30 to 39	14
40 to 49	27
50 to 59	21
60 to 69	12
70 to 79	1

Forty-eight, or 57 per cent, were between the ages of 40 and 60 years. The youngest was 16 and the oldest 73 years. Seventy patients were white, eleven were Negroes, and in three the race was not stated. Seventy were married, fourteen, or 16.6 per cent, were single. (This corresponds to Lynch's 17 per cent and Pemberton's 19 per cent.) Only eight, or 11.4 per cent, of the married women were sterile. This is much lower than the 31 per cent reported by Lynch and the 22 per cent in Pemberton's series. Of the sixty-two women who had conceived, eight, or 13 per cent, did not carry their pregnancies to term. In four cases the parity was not stated. Thirty-one patients had passed the menopause, in three of these the amenorrhea had been induced by radiation. There was a family history of cancer in ten instances or 13.6 per cent of seventy-five cases in which this was recorded in the history. This is far below the 40 per

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cent noted by Lynch. Such figures may be unreliable since the accuracy of the patient's knowledge of her family medical history is often open to question. Eight patients or 9.8 per cent of eighty-one in whom chest examinations were recorded had pleural effusions. Two of these had minimal pulmonary tuberculosis. Ureteral obstruction was noted in five patients although only a few had studies of the upper urinary tract. The blood sedimentation was rapid in thirty-eight and normal in fourteen of these cases where it was recorded.

Twenty-three patients had previous operations. Three had intrauterine radium for benign bleeding thirteen, ten, and seven years previously. Three had vaginal plastic operations (one with hernia repair) nine, seven, and three years previously, and one had a small dose of radium to the cervix four years before for a lesion that proved to be benign. Four had abdominal pelvic operations from fifteen to twenty years before. Three patients had abdominal operations one year previously. One of these had an umbilical hernia repaired, one had an operation for an ovarian abscess, and one had a supravaginal hysteromyomectomy. The latter patient, who was 37 years of age was operated upon on our service, the ovaries appeared to be normal and were conserved. She had an inoperable bilateral solid carcinoma when readmitted one year later. Seven patients had mastectomies performed from four to twenty-three years previously, but we do not know how many actually had cancer of the breast. One had a cholecystectomy four years before and one had a resection of her stomach sixteen years before coming under our care. Two patients had refused operation for pelvic tumors, two and ten years previously.

The chief symptoms mentioned were pain in fifty-three instances and enlargement of the abdomen in fifty-nine, a large proportion of patients exhibiting both. Nausea and vomiting, loss of weight, backache, weakness, and dyspnea were mentioned less often. Eleven, or 14 per cent of the patients complained of bleeding; six of these had associated uterine fibroids. The duration of symptoms from time of onset until admission to the hospital may be listed as follows:

Less than 1 month	8
1 to 3 months	13
3 to 6 months	13
6 to 12 months	21
12 or more months	19
Not stated	10

Thirty-seven patients complained of vague gastrointestinal symptoms other than constipation for six months or longer.

It has been our policy to operate upon all patients whose physical condition would permit of surgery, even though the growth appeared to be extensive. The primary tumor was removed whenever possible. The omentum was excised only if involved by a growth that was otherwise limited to the pelvis. The tendency to attempt surgery in many advanced cases, in part explains our mortality rate of 17 per cent, since nine of the fourteen postoperative deaths occurred in patients with very far advanced malignancy. The following operative procedures were done:

Supravaginal hysterectomy and bilateral salpingo-oöphorectomy	18
Supravaginal hysterectomy and unilateral salpingo-oöphorectomy	3
Total hysterectomy and bilateral salpingo-oöphorectomy	4
Bilateral salpingo-oöphorectomy	10
Unilateral salpingo-oöphorectomy	14
Exploratory only	33
Died without operation—autopsied	2

Three patients who originally had postoperative x-ray therapy were reoperated upon later. In one a recurrence was removed nine years after the original operation. The others, in both of whom only an exploratory operation

was done originally were still inoperable after one and eleven years, respectively. Unilateral oöphorectomy was done in seventeen patients, one of whom had one ovary removed twenty years previously. In three of these the growth was extensive and in five the patient's condition did not warrant further surgery. Of the eight in which an apparently normal ovary was deliberately conserved, one is untraced, one died of an undetermined cause at the end of eight years, having had a normal pregnancy four years before, and six are living and free of disease for more than five years.

We have studied our cases in the light of the four outstanding factors that generally are regarded as governing the end results in ovarian carcinoma, (a) the extent of the growth or the operability, (b) the grade of malignancy, (c) the histologic type of tumor, and (d) the influence of x-ray therapy on the lesion. Throughout the study, where possible, we attempt to show the interrelationship of these factors.

The group of eighty-four primary adenocarcinomas have been classified as either serous or pseudomucinous. Where the growth was anaplastic (Grade III), occasionally there was some doubt as to the correct histologic diagnosis but as a rule such cases appeared to be serous and were classified as serous carcinomas. Although the gross structure of the tumors has been regarded as of secondary importance we have further divided them into cystic, partly solid and partly cystic, and solid growths. This has been done in recognition of the fact that the tumors of solid consistency are more actively malignant than those whose structure is largely cystic or papillary.

Grade of Malignancy

Most reports indicate that the best results can be expected in those patients with well differentiated tumors. On the other hand "grading" is generally thought to be of little value in prognosis of ovarian carcinoma. However, as Taylor suggests "if the recognition and segregation of the well differentiated group may be termed 'grading' then the grade of malignancy in ovarian carcinoma is of enormous prognostic significance." It is from such a viewpoint that we have divided our cases into three histologic grades of malignancy as suggested by Taylor and as employed by us in a previous contribution to this subject.

Grade I or Low Grade Malignancy.—Tumors in which well differentiated columnar epithelium lined the glands and cystic spaces, the adult structure being maintained throughout except in occasional areas where there was slight infiltration, a piling up of epithelial cells into two or more layers and slight nuclear changes.

Grade II or Intermediate Grade Malignancy.—Tumors that are actively malignant but which show definite glandular or papillary structures.

Grade III or High Grade Malignancy (Anaplastic).—Undifferentiated epithelial cells with marked nuclear changes growing in strands or solid areas with little or no glandular or papillary structure.

Grade I Carcinoma.—(Table I.) Twenty-one cases; fourteen serous and seven pseudomucinous adenocarcinomas. Eleven patients are living from five to twenty-four years. Ten of these are free of disease and one, in which an exploratory operation was done twelve years ago and who was reoperated upon one year ago, still has evidence of extensive pelvic malignancy. Seven of the

TABLE I. SUMMARY OF RESULTS—GRADE I MALIGNANCY

	PATIENTS	UNILATERAL	BILATERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN FIVE YEARS		DEAD		UNTRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	INCOMPLETE X-RAY
Serous Papillary Adenocarcinoma										
Completely operable	6	3	3	2	1	0	1	1 1 yr. Cause?	0	1
Incompletely operable	5	1	4	3	0	0	0	1 6⅓ yr.	1 P.O.D.	0
Exploratory	3	0	3	1 12 yr. c̄ disease	0	1 1½ yr. c̄ disease	0	1 6 yr.	0	0
Total	14	4	10	6	1	1	1	3	1	1
Pseudomucinous adenocarcinoma										
Completely operable	5	5	0	2	2	0	0	0	1 8 years Cause?	0
Incompletely operable	2	1	1	0	0	1 3 yr. inadequate	0	1 6½ yr.	0	0
Exploratory	0	0	0	0	0	0	0	0	0	0
Total	7	6	1	2	2	1	0	1	1	0
Grand Total	21	10	11	8	3	2	1	4	2	1

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TABLE II. SUMMARY OF RESULTS GRADE II MALIGNANCY

	PATIENTS	UNILATERAL	BILATERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN 5 YEARS		DEAD		UNTRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY
Serous Papillary Adenocarcinoma										
Completely operable	4	3	1	1	0	0	0	1 4 yr.	2 P.O.D.	0
Incompletely operable	10	4	6	2 1 c̄ recur 7 yr.	0	0	0	4 1-3 yr.	4 3 P.O.D.	0
Exploratory	5	0	5	0	0	0	0	3 2 inadequate	2	0
Total	19	7	12	3	0	0	0	8	8	0
Pseudomucinous Adenocarcinoma										
Completely operable	1	1	0	1	0	0	0	0	0	0
Incompletely operable	2	0	2	0	0	0	0	2 1 inadequate	0	0
Exploratory	1	0	1	0	0	0	0	1 3 yr.	0	0
Total	4	1	3	1	0	0	0	3	0	0
Grand Total	23	8	15	4	0	0	0	11	0	0

five-year survivors had tumors of the serous type of which three were completely operable and three incompletely operable, while in one only an exploration was possible. All but one received deep x-ray therapy. In the three completely operable cases the growth was unilateral. The four remaining five-year survivors had unilateral, completely operable pseudomucinous tumors two of whom received deep x-ray therapy.

Three patients with Grade I tumors are living for less than five years after operation. Two had tumors of the serous type, one was removed completely but only exploration was possible in the other. The third patient had an incompletely operable pseudomucinous tumor. The completely operable patient received no x-ray therapy while the other two received only a small amount.

Six patients with Grade I malignancy are dead, and one is untraced. Four of these had tumors of the serous type of which one was completely operable, two incompletely operable and one had only an exploration. One patient with an incompletely operable tumor died as a result of the operation. The other three received deep x-ray therapy. The patient whose tumor was removed completely died one year later of an undetermined cause, but the other two died of malignancy after six and one-half years. Two patients who died had pseudomucinous tumors. One whose tumor was completely removed, subsequently had a normal pregnancy, but died eight years after operation of an undetermined cause. The other with an incompletely operable tumor received x-ray therapy but died of malignancy after six and one-half years.

Grade II. Carcinoma.—(Table II.) Twenty-three cases; nineteen serous and four pseudomucinous adenocarcinomas. Four are living. Three are free of disease from five to twenty years after operation, and one has a recurrence in the cervix after seven years. Three of the four survivors had bilateral tumors of the serous type. In one of these the growth was removed entirely but in two instances the operation was incomplete. The fourth survivor had a completely operable, unilateral pseudomucinous adenocarcinoma. All four received deep x-ray therapy. Eighteen patients with tumors of Grade II malignancy are dead (four as a result of the operation), and one is untraced. Eleven of these received deep x-ray therapy, but the dosage was adequate only in seven. Of these receiving a full course of x-ray, one patient with a completely operable unilateral cystic and solid tumor of the serous variety survived for four years and one with an incompletely operable bilateral solid growth of the same type lived for three years, one patient with an inoperable serous tumor died in thirteen months, and two others with partly cystic and partly solid tumors died of malignancy after one and one-half years and six months, respectively. One patient with an inoperable pseudomucinous tumor survived for three years, and one with incompletely operable pseudomucinous growth died of malignancy after one and one-half years. The four with inadequate radiation all had advanced serous tumors and died of malignancy in less than six months. Of the seven patients who did not receive x-ray therapy four died as a result of the operation, one with incompletely operable tumors and two in whom only exploration could be done survived for eight months, two months, and eleven months, respectively.

Grade III Carcinoma.—(Table III.) Forty cases; thirty-nine serous and one pseudomucinous carcinoma. One patient is living and free from evidence of malignancy twenty-one years after complete removal of a unilateral serous papillary adenocarcinoma (partly solid and partly cystic) followed by deep x-ray therapy. Two are living and free of disease for less than five years. In one of these the tumor was unilateral with local extension, not all of which could be removed and the other had bilateral tumors with a nodule in the omentum, completely operable. The first patient received x-ray therapy, the second did not. Thirty-five are dead, ten postoperatively. Of the twenty-five

who survived the operation seventeen received x-ray therapy and eight did not. In eight of these treated by x-ray the tumors had been removed in part and in the others nothing more than an exploratory section was done. Of the former group one died in eight months, two died in one and one-half years, one in one and three-fourths years, one in two and one-half years, and three survived for three years, although one had inadequate therapy. Among the nine patients who had only exploratory operations, one is untraced and two with inadequate x-ray survived less than two months. The others died in seven months, 7 months, ten months, one and one-half, one and one-half, and one and two-thirds years, respectively. In eight of the nine patients who survived the operation but died without x-ray therapy the growth was altogether inoperable, while in one only an incomplete operation was done. One of these survived for ten months, but the others all died of malignancy in less than four months.

TABLE III. SUMMARY OF RESULTS GRADE III MALIGNANCY

SEROUS PAPILLARY ADENOCARCINOMA	PATIENTS	UNILATERAL	BILATERAL	LIVING 5 TO 21 YEARS		LIVING LESS THAN 5 YR.		DEAD		UNTRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY
Completely operable	3	3	0	1	0	0	1	0	1	0
Incompletely operable	11	5	6	0	0	1 4 yr.	0	8	2 1 P.O.D.	0
Exploratory	25	0	25	0	0	0	0	8 3-3 yr.	15 8 P.O.D.	2
Total	39	8	31	1	0	1	1	16	18	2
Pseudomucinous exploratory	1	1	0	0	0	0	0	0	1 P.O.D.	0
Grand Total	40	9	31	1	0	1	1	16	19	2

Twenty-one of the entire group of eighty-four patients with primary adenocarcinoma of the ovary are living. Fourteen of these had tumors of Grade I malignancy, four had Grade II, and three had Grade III malignancy.

Sixty-eight of the eighty-four patients were treated before Oct. 1, 1941, and therefore are eligible for five-year study. In Table IV the five-year results in each of the three grades of malignancy are presented in relation to the histologic type of the tumors. It will be noted that the five-year salvage of 20.5 per cent is due largely to the fact that ten of the fourteen patients who are free of disease had tumors of Grade I malignancy. The five-year results in relation to grade of malignancy alone are presented in Table V. The high percentage of survivors in the Grade I group is very striking. The effect of this Grade I on the five-year results is seen even more clearly when the cases in Grade II and Grade III are combined. The total is fifty-two, or 73.5 of the sixty-eight cases that are eligible for five-year study, and only four, or 7.7 per cent are free of malignancy for five or more years.

These figures emphasize the striking influence of "grading" in the prognosis of ovarian cancer and are in line with the findings of Taylor who reported twelve cured among thirty-six Grade I cases, but only two among fifty-two undifferentiated types. Although the influence of the well-differentiated tumors is well recognized generally, failure to take these into consideration undoubtedly accounts for the high percentage of cures that sometimes are reported. Although many believe that segregation of the actively malignant tumors into Grade II and Grade III malignancy probably has little prognostic value, our experience based on results shown in Tables I to III and in Table V suggest

TABLE IV. RESULTS IN SIXTY-EIGHT CASES ELIGIBLE FOR FIVE-YEAR STUDY

	PATIENTS	LIVING AND FREE OF DISEASE FIVE YEARS PLUS	
		NUMBER	PER CENT
Serous Papillary Adenocarcinoma Grade I	10	6	60
Pseudomucinous Adenocarcinoma Grade II	6	4	66.6
Serous Papillary Adenocarcinoma Grades II and III	48	3	6.2
Pseudomucinous Adenocarcinoma Grades II and III	4	1	25
Total	68	14	20.5

TABLE V. RESULTS IN RELATION TO GRADE OF MALIGNANCY IN SIXTY-EIGHT CASES ELIGIBLE FOR FIVE-YEAR STUDY

MALIGNANCY	TOTAL CASES		FREE OF DISEASE FIVE YEARS	
	NUMBER	PER CENT	NUMBER	PER CENT
Grade I	16	23.5	10	62.5
Grade II	19	27.9	3	15.8
Grade III	33	48.5	1	3.0
Grades II and III	52	73.5	4	7.7

that we may expect somewhat different results in these two groups. This difference, however, may be due to the fact that there is a definite relationship between the grade of malignancy and the extent of the growth in many of our cases in these two groups. As a rule the growth was much further advanced in Grade III cases; in twenty-six, or 65 per cent, of forty patients in this group, only exploration could be done—while only six, or 26 per cent, of the Grade II cases were inoperable. In the incompletely operable patients the growth as a rule was less extensive in Grade II than in those with Grade III carcinoma. The three living patients who had Grade III cancer all had unilateral completely operable papillary cysts.

The high percentage of survivors in the group with Grade I malignancy may be due to the well-known difficulties in histologic diagnosis in this group. Errors are inevitable, and the desire to err on the side of safety perhaps accounts for the inclusion of some cases of doubtful malignancy in this group. Taylor and others have reported cases in which careful follow-up observations have made it obligatory that the original diagnosis be changed. Two of our cases illustrate this difficulty.

M. Y., aged 32 years, had bilateral salpingo-oöphorectomy performed at the Jefferson Hospital on Dec. 11, 1923, for bilateral papillary ovarian cysts which involved the right broad ligament. The histologic diagnosis was papillary cystadenoma of the ovaries (nonmalignant). Because of the grossly invasive nature of the growth, the patient was given deep x-ray therapy prophylactically. She remained well and free from evidence of disease until May, 1932. Reoperation revealed a cauliflowerlike growth about the size of an orange originating between the layers of the right broad ligament and extending on to the adjacent peritoneum. The mass was excised and she was again given x-ray therapy (4,500 r in air over four portals). The histologic diagnosis was papillary adenocarcinoma. When last examined on Jan. 2, 1940, she was well and free from palpable evidence of malignancy. In a recent communication from another city she reported that she is in excellent health.

M. H., aged 23 years. Bilateral salpingo-oöphorectomy and supravaginal hysterectomy was done on Jan. 3, 1935, for large bilateral ovarian tumors which

were adherent. The histologic diagnosis was pseudomucinous cystadenoma of both ovaries, malignancy doubtful. X-ray therapy was withheld until six months later when a small mass was noted in the cul-de-sac. The diagnosis was changed to pseudomucinous cyst adenocarcinoma.

Extent of the Growth

The gross extent of the disease, of course, is recognized as the most important factor in prognosis. We have divided our cases into three groups according to their operability, namely, those in which all of the tumor was removed (completely operable); those in which the tumor was removed only in part (incompletely operable); and those in which only an exploratory operation could be done. Such a grouping has the advantage of simplicity, but fails to take into account such influences as rupture of the tumor during operation, or adhesions in the completely operable group, and the extent of the disease in those that are incompletely operable.

Table VI presents the results in the eighty-four cases of adenocarcinoma from the viewpoint of the gross extent of the disease and in relation to the type of tumor and the influence of x-ray therapy. The tumor was completely operable in nineteen, or 22.6 per cent. Ten of these are free of evidence of disease from five to twenty-four years, and two for less than five years. Thirty, or 35.7 per cent, were incompletely operable, of which only four were free of gross disease for more than five years. Thirty-five, or 41.6 per cent were inoperable, but one of these is alive with extensive disease still present twelve years, and one is alive one and one-half years after surgical exploration. The relation of grade of malignancy to the extent of the growth has been discussed in the preceding section and indicated in the accompanying tables.

TABLE VI. SUMMARY OF RESULTS IN RELATION TO EXTENT OF GROWTH AND TYPE OF TUMOR

	PATIENTS	UNILATERAL	BILATERAL	LIVING 5 TO 24 YEARS		LIVING LESS THAN 5 YEARS		DEAD		UNTRACED
				X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	
Serous Papillary Adenocarcinoma										
Completely operable	13	9	4	4	1	0	2	2	2	2
Incompletely operable	26	10	16	5 1 with disease	0	1	0	13	7	0
Exploratory	33	0	33	1 with disease	0	1 with disease	0	12	17	2
Total	72	19	53	10	1	2	2	27	26	4
Pseudomucinous Adenocarcinoma										
Completely operable	6	6	0	3	2	0	0	0	1	0
Incompletely operable	4	1	3	0	0	1	0	3	0	0
Exploratory	2	1	1	0	0	0	0	1	1	0
Total	12	8	4	3	2	1	0	4	2	0
Grand Total	84	27	57	13	3	3	2	31	28	4

Table VII presents the results in relation to the extent of the growth in the sixty-eight cases that are available for five-year study.

TABLE VII. RESULTS IN RELATION TO EXTENT OF GROWTH IN SIXTY-EIGHT CASES ELIGIBLE FOR FIVE-YEAR STUDY

			FREE OF DISEASE FOR FIVE YEARS	
	PATIENTS	PER CENT	PATIENTS	PER CENT
Completely operable	18	26.5	10	55.5
Incompletely operable	20	29.4	4	20.0
Exploratory	30	44.1	0	0.0
Total	68	100	14	20.5

Type of Tumor

Adenocarcinoma.—There were eighty-four cases of adenocarcinoma; of these, seventy-two, or 85.7 per cent, were serous, and twelve or 14.3 per cent, were pseudomucinous adenocarcinomas. The relation of the grade of malignancy, the extent of the growth, and the influence of x-ray therapy, to the end results in these two groups as shown in Tables I to VII have been discussed previously. Although the total number of pseudomucinous tumors is small, our results substantiate the frequently stated view that these tumors are less malignant than the serous variety among which there is a much larger proportion of incompletely operable and inoperable tumors.

Of the sixty-eight patients who were treated more than five years ago, fifty-eight had serous papillary adenocarcinomas of whom nine or 15.5 per cent, are living and free of disease for more than five years, while of the ten with pseudomucinous tumors, five, or 50 per cent, have survived for five or more years without recurrence.

It is well known that at least three pathologic entities based on the gross characteristics of the tumor which are encountered frequently are of considerable prognostic importance. These are the papillary cysts, the partly solid and partly cystic tumors, and the solid tumors. From Table VIII it will be seen that twelve of the sixteen patients who are living for five or more years had papillary cysts (ten of these were of Grade I malignancy). Only four of the thirty-seven with partly solid and partly cystic tumors have survived more than five years, and all of the eighteen who had solid carcinomas are dead.

TABLE VIII. RESULTS IN RELATION TO GROSS TYPE OF TUMOR

				LIVING 5 TO 24 YEARS		LIVING LESS THAN FIVE YEARS		DEAD		
	PATIENTS	UNILATERAL	BILATERAL	X-RAY	NO X-RAY	X-RAY	NO X-RAY	X-RAY	NO X-RAY	UNTRACED
Papillary cystadenocarcinoma	20	12	8	9 2 with disease	3	0	0	5	3 3 P.O.D.	
Solid and cystic adenocarcinoma	37	10	27	4	0	3	2	14 4 inadequate	13 1 8 yr. 8 P.O.D.	1
Solid adenocarcinoma	18	3	15	0	0	0	0	8 2 inadequate	9 4 P.O.D.	1
Undetermined	9	1	8	0	0	0	0	5 3 inadequate	3	1

Granulosa Cell Tumors.—There were ten cases, or 9.3 per cent, of the entire group of 107 cases of malignant tumors of the ovary. Three are dead. One died of cerebrospinal syphilis three years after operation, one died eight weeks after operation as a result of x-ray damage to the large bowel, and one whose tumor regressed on three occasions following x-ray therapy died of malignancy eight years after incomplete operation. The latter two were regarded originally as anaplastic carcinomas. They were included in a previous report emphasizing the value of x-ray therapy in ovarian cancer. Four are living and free of disease, three for more than five years. One of these who has survived eleven years was given x-ray therapy under the mistaken diagnosis of anaplastic carcinoma. Three patients in this group are untraced.

Ovarian Carcinoma Associated With Adenocarcinoma of Endometrium.—There were seven cases, or 6.5 per cent, of the entire group. The growth apparently originated in the uterus in all, although in two instances this was somewhat doubtful. In one of these there was an anaplastic squamous cell carcinoma of the cervix with a solid papillary adenocarcinoma of the ovary in which some areas showed a lesion identical with that in the cervix. The other patient had carcinoma involving the entire endometrium and a unilateral papillary adenocarcinoma of the ovary, some areas of which contained epithelial elements resembling pseudomucinous carcinoma. This was regarded as probably of endocervical origin. Two patients had been treated with intrauterine radium for endometrial carcinoma two and four years before operation for the ovarian tumor, and one had received x-ray therapy without curettage on two occasions during the previous ten years for supposed benign bleeding. Six patients are dead, one as a result of operation. Two died within six months, the other three each of whom received deep x-ray therapy lived one and one-half, three and three-fourths and seven years, respectively. One patient is living and free of evidence of disease one and one-half years after total hysterectomy and bilateral salpingo-oöphorectomy followed by deep x-ray therapy.

Special Group.—There were two dysgerminomas—one patient was a girl 16 years of age, and the other was twenty-eight years of age. They have remained well for twenty-four years and three years, respectively. The 16-year-old patient was reported in 1925 by Dr. Lewis C. Scheffey as a sarcoma of the ovary. Two adenocarcinomas developed in teratomas. Both patients are dead, one died of cardiac failure three weeks after complete removal of bilateral tumors, the other survived for one year after removal of a large adherent solid tumor followed by x-ray therapy. One patient who had a Brenner tumor was well when last examined eight years after operation. She is untraced for seven years. One patient with a Krukenberg tumor died within three months after operation.

X-ray Therapy

The factors used in administering x-ray therapy have varied somewhat since our first case was treated in 1924. Two methods have been used. Prior to August, 1927, massive doses were given at a single sitting at right angles to one of three or four pelvic ports. The amount given was that which the skin would tolerate, and the entire course was completed in three or four days. The factors were 3 milliamperes, 170 to 200 kilovolts filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin target distance through ports 16, 19, or 20 cm. square. An erythema was obtained with 270 milliampere minutes of treatment. After August, 1927, the saturation method was used.

Treatment was given usually over four ports, though occasionally in thin persons only three were used.

After January, 1925, the following factors were used: 20 to 30 milliamperes, 175 to 200 kilovolts, filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin target distance, through ports 16, 19, 20 cm. square. The erythema value from January, 1925, to August, 1930, was 970 r, and since August, 1930, has been 800 r. There has been no major change since 1930, although in recent years the four fields have been reduced to 10 by 15 cm. except in patients with broad pelves when they are widened to 15 by 15 cm. Previous to 1942 patients were treated on alternate days, so that at the end of four weeks the effective depth dose was from 1,600 to 2,000 r. Since that time they have been treated daily with 125 to 250 r, depending on tolerance. When disease is known to be widespread, four additional fields cephalad to the pelvic ports are used, or two fields may be substituted covering the area from xiphoid to pelvis. With very large fields and with small fields in obese women, the T.S.D. is increased to 80 cm. The total dosage given is 2,000 to 3,000 r per field, except with large fields when it is reduced to 1,000 to 1,500 r. Any patient who receives less than 1,200 r to each of four 10 by 15 cm. fields is regarded as inadequately treated. In recent years there has been insistence on small daily dosage with attention to avoid diarrhea and vomiting with less tendency to multiple series of treatments.

We have urged x-ray therapy in all patients whose general physical condition warrants it, except those with extensive upper abdominal metastasis. It is of utmost importance that the roentgenologist be acquainted with the location and gross extent of the malignancy so that he may outline the fields and direct the rays to the best advantage. There is some risk of damage when the treatment is pushed to the limit. One of our patients developed agranulocytosis and another an ulcerative colitis.

When the results from x-ray therapy are studied in relation to the grade of malignancy, it will be seen as noted previously that in Grade I (Table I), eight of eleven five-year survivors received deep x-ray therapy. In three of these the tumor was not completely removed, while in one only an exploratory operation was done. Four of these patients are living for more than ten years, one with evidence of disease still present. All three who survived five years without x-ray therapy had completely operable tumors. Among those who have died following x-ray therapy three survived for six and one-half years. However, since patients with tumors of this Grade of malignancy are known to survive for more than five and occasionally for more than ten years without x-ray, its value in this group is uncertain. In Grade II (Table II) malignancy the influence of x-ray therapy was more definite, since two of the five-year survivors who were so treated had incompletely operable tumors—although one now has a recurrence. The duration of life was probably prolonged in seven other patients in this group. In Grade III (Table III), one patient with an incompletely operable tumor who received x-ray is free from evidence of malignancy for four years after operation. Among seven who survived the operation but died subsequently, the duration of life was apparently prolonged.

In relation to the gross extent of the disease the value of x-ray therapy should be demonstrated best in those patients whose tumors were partly or altogether inoperable. Six such patients are living for five or more years, although the significance of this is mitigated by the fact that in four of these the tumors were of Grade I malignancy. One of the others now has a recurrence, and the other is apparently free of malignancy after nine and one-half years. To compare the duration of life in the patients who received x-ray therapy with those who did not would give an inaccurate impression of the value of the x-ray, since in most instances those who were not so treated had metastasis to the liver or were too ill to tolerate the treatment. All of these died within one year, most of them within six months. Among fourteen patients with partly operable tumors of Grade II and Grade III malignancy who have died following x-ray therapy, three lived for six months; one for eight months; three for one and one-half years; one for one and two-thirds years; one for one and three-fourths years; one for two and one-half years; and four for three years. Of thirteen with inoperable tumors who died following x-ray therapy, four lived less than three months; four lived for six to twelve months; two for one and one-half years; one for one and two-thirds years; one for three years; and one is untraced. It would appear that the x-ray probably prolonged the life of some of these patients.

Our experience with x-ray therapy in pseudomucinous tumors where the growth was partly or completely inoperable is limited to three patients. One of these who had a partial operation survived for six and one-half years, and another for one and one-half years, while one whose growth was inoperable lived three years, during which time she had x-ray therapy on two occasions. However, there is some question as to whether this would be regarded as a pseudomyxoma peretonei. In considering the serous tumors, if we eliminate all those of Grade I malignancy and all whose tumors were completely removed, we have left twenty-six patients in whom the effect of x-ray therapy might be evaluated. As pointed out above, the x-ray probably prolonged the life of some of these patients. However, only three of this group are alive, and one of these has a recurrence after seven years. One is living four years and the other nine and one-half years without evidence of malignancy. The latter had bilateral tumors limited to the pelvis but not completely operable. In all other patients with serous tumors who are living more than five years without evidence of disease, the growth was either completely removed or the tumor was of Grade I malignancy.

Summary of Results

Table IX presents a summary of the end results in the 107 cases of malignant ovarian tumors. The five-year survival of 44 per cent in the granulosa cell group is influenced by the three untraced cases which are counted as dead. However, the 22 per cent of five-year survivors in the entire group approximates the 20.5 per cent of survivors in the primary adenocarcinoma group.

TABLE IX. RESULTS IN 107 MALIGNANT TUMORS OF THE OVARY

MALIGNANT TUMORS OF THE OVARY	TOTAL PATIENTS		PATIENTS ELIGIBLE FOR FIVE-YEAR STUDY		
				FREE OF DISEASE FIVE YEARS PLUS	
	NUMBER	LIVING—NO MALIGNANCY	NUMBER	NUMBER	PER CENT
Primary adenocarcinoma	84	18	68	14	20.5
Adenocarcinoma secondary to uterine cancer	7	1	4	0	0
Adenocarcinoma in a teratoma	2	0	2	0	0
Granulosa cell tumors	10	4	9	4	44.4
Dysgerminoma	2	2	1	1	100
Krukenberg tumor	1	0	1	0	0
Brenner tumor	1	Untraced after 8 yr.	1	0	0
Total	107	25	86	19	22.0

All untraced patients are counted as dead.

Comment

Operability and grade of malignancy are undoubtedly the factors that govern the percentage of survivals for five or more years. So far as type goes the papillary cysts are the most favorable and if they are completely operable one may safely predict that at least 50 per cent will be alive and free of disease for more than five years. On the other hand, it is agreed by all that the number of five-year survivors among those who have actively malignant tumors of the partly cystic and partly solid, or of the solid type is pitiably small. This result is influenced by the fact that the vast majority of such tumors do not come under observation until the growth is far advanced. The difficulties in achieving an early diagnosis in carcinoma of the ovary seem almost insurmountable. Many are "silent" or nearly so. Yet we have found in reviewing the histories that 37 per cent of our patients had abdominal symptoms, mostly referable to the gastrointestinal tract for six months to several years before a pelvic examination was made. One patient, the sister of a physician, was given "samples" for "indigestion" for three years before her abdomen began to swell. Another had been treated for "colitis" for four years and had a complete medical survey in a hospital less than one year before large bilateral ovarian tumors were discovered on routine pelvic examination. It is not uncommon for abdominal enlargement to be the first sign of trouble.

Such instances suggest that repeated routine pelvic examinations in all women may be needed to solve the problem of early diagnosis but even then some may be overlooked. The studies of Dr. Catharine Macfarlane are very interesting in this respect. Among 1,370 apparently healthy women who presented themselves for routine pelvic examination and of whom 670 have reported for re-examination every six months for nine and one-half years, one ovarian carcinoma was encountered. This tumor which was reported to be the size of an orange was not present when the patient was examined six months previously. That a malignant tumor of the ovary may develop with great rapidity is indicated by the far advanced carcinoma that was found in one of our patients

one year after supravaginal hysteromyomectomy at which time the ovaries were examined and noted to be normal.

Peritoneoscopy undoubtedly has a place in the diagnosis of ovarian malignancy as noted by Pemberton and by Meigs but unless it is utilized before abdominal distention and persistent pain develop it will be of no avail. In the few cases in which we have used it the symptoms and the physical examination indicated a far-advanced lesion. There is considerable doubt in our minds about the value of this method in early cases, since the ovary is often difficult to visualize if it is not enlarged, especially in obese women. However, in some instances this handicap can be overcome if the procedure is combined with vaginal palpation.

Periodic routine pelvic examination would undoubtedly point the way to earlier diagnosis in many instances. Macfarlane's case illustrates the wisdom of making such an examination at six-month intervals. When some enlargement of the adnexa is noted under such circumstances it may present a difficult problem. In women of childbearing age enlargements of the ovary of approximately 5 or 6 cm. in diameter are most likely physiologic in origin. The prompt operation and radical removal of such ovaries that is sometimes practiced is to be deplored. On the other hand, when such enlargements persist, or show evidence of progressive enlargement, especially in women of menopausal age, an exploratory incision is safer than prolonged watchful waiting. Such a procedure also probably would be wise in certain suspected patients with vague abdominal symptoms, when after thorough study and consultation with an internist no other cause is found for the persistent symptoms.

If malignant disease is to be detected at an early stage in more than an occasional patient, routine periodic pelvic examinations will have to be carried out in large numbers of women and supplemented at times by special studies, and occasionally by an exploratory abdominal incision. The success of such a program will depend upon the ability and care of the family doctor as well as the gynecologist.

The author is indebted to Dr. Theodore P. Eberhardt and Dr. Hugh O'Neil of The Department of Radiotherapy, Jefferson Medical College Hospital, for the data pertaining to x-ray therapy.

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Discussion

DR. FRANK PEMBERTON, Boston, Mass.—The symptomatology of this disease is of little value in diagnosis, for it is usually so advanced when seen as to be unmistakable. However, if a patient at or after the climacteric complains of a feeling of pressure in the pelvis and rectum and has no palpable masses, but does have some tenderness in the posterior cul-de-sac, we always think of the everting papillary ovarian carcinoma which has spread to the peritoneum early.

We agree with Dr. Montgomery that every case should be operated on and as much of the tumor removed as possible. It is interesting that in thirty-five out of eighty-four cases nothing more than exploration was done, for, in the series of 149 cases from the Free Hospital for Women that I reported in 1940, we had been able to remove all or part of the pelvic organs in 141, with a mortality of 6.6 per cent, as against the Jefferson Hospital's 17 per cent. I think this can be accounted for by the fact that our series included many private patients who seek treatment earlier as a rule than those going to outpatient clinics.

Dr. Montgomery's finding that the more solid the tumor is the more malignant it is agrees with other series of cases. Grading these tumors, especially the borderline ones, is a difficult proposition with a large personal equation as was brought out by the discussion in 1940, but in general our results, so far as five-year survivals in the various grades is concerned, corresponds with the readers'. This is also true regarding the greater malignancy of the serous type as compared to the pseudomucinous.

End results are difficult to evaluate, for one can rarely feel sure that the patient is free of tumor, and therefore I believe that five- and ten-year survival figures of all patients are more interesting than those dealing with patients free of disease.

Dr. Montgomery gives 20.5 per cent for the latter classification. If he has the figure for the former I hope he will tell us what it is. There are several reports of 30 per cent to 40 per cent five-year survival, including the 32 per cent at the Free Hospital for Women, but we realize that 10 per cent at least of those survivors have active disease.

We are all interested in the value of radiation treatment. Dr. Malcolm S. Allan is going over our cases again and I am indebted to him for the following figures.

1930 to 1942.—Radiated cases, x-ray alone, 57; radium alone, 3; x-ray and radium, 9; all were operated on first. Forty-one (59 per cent) showed gross metastases. Grade I, 39 per cent; Grade II, 30 per cent; Grade III, 31 per cent. Dead, forty-two (60 per cent) at an average of three and eight-tenths years; alive, twenty-seven (40 per cent) five years or more.

Ten of the twenty-seven cases still living had gross metastases at the time of operation. They have survived five to thirteen years, and one has evident growth.

The 40 per cent survival rate is encouraging, but this is a small series of cases and no conclusions are very valuable.

X-ray treatment, in my experience, does seem to decrease the rapidity with which ascites accumulates.

DR. EDWARD SCHUMANN, Philadelphia, Pa.—Dr. Montgomery's survival figures, as has been said, compare very favorably with others. I must confess to a great deal of skepticism myself regarding survival figures in malignancy. I would like to reaffirm the difficulties of grading these cases and really ascertaining whether or not they are malignant. If we are dealing with the tumor which we have always called cystadenoma, but which we now term endosalpingioma, and which tumors are of Müllerian origin, the lining being of the same pattern and corresponding to that of the Fallopian tube. Necessarily the epithelial lining of these papillary cysts changes with the menstrual cycle of the woman if she be in the menstrual age, and the ordinary skilled pathologist in a hospital has great difficulty in determining whether or not they are malignant. There is a papillary form, an invasive form of this growth, which Dr. Howard Taylor has called semimalignant, and I feel when such tumors occur in any set of figures one doesn't know whether it was ever malignant or not. That is also true of the pseudomucinous cystadenoma where there may well be perineal implants without malignancy. So that I am never convinced that a papillary tumor is malignant, and when we have succeeded in having a survival I do not know whether I have succeeded in curing a carcinoma or merely helped a benign condition.

As to the question of radical operation for a presumably malignant tumor, Dr. Montgomery suggested the Wertheim operation on the side on which the ovarian growth is to be removed. This, I think, is an extremely wise procedure. There also arose the question of the removal of the opposite healthy ovary in a young woman who possesses a papillary cyst of one type or another. Many are convinced that the healthy ovary should not be removed, pend-

ing a most careful pathologic examination of the specimen. This cannot be carried out quickly so that it becomes obligatory to subject the patient to another operation if the ovarian tumor is found to be malignant.

DR. ARTHUR H. CURTIS, Chicago, Ill.—It just occurred to me that you may be interested in the story of a patient of Dr. Watkins' and myself. When we opened the abdomen it looked like a very hopeless affair, implants from a solid ovarian growth spread throughout the abdomen, associated with ascites. We removed every thing available, as was a little unusual for us to do in those earlier days. The patient lived very satisfactorily for ten years. Then she had a recurrence and we removed again as thoroughly as possible. She lived for another five years and then died of malignancy. It shows we should never give up.

DR. CURTIS F. BURNAM, Baltimore, Md.—I agree fully that x-ray is not of a great deal of use in treating carcinomas of the ovary, but there seems to be some exceptions. I had a case referred to me by one of Baltimore's gynecologists where he had removed a solid carcinoma of the ovary. For a year and one-half this patient seemed quite well, and then she developed a mass in the cul-de-sac, a hard, fixed mass. An exploratory operation was done. We made a diagnosis of recurrent carcinoma but no specimen was taken at the last operation. That patient was treated by x-ray. The lesion cleared up and there has been no return in eight years.

DR. MONTGOMERY (Closing).—I think our series includes an unusually high percentage of hopelessly inoperable patients. Twenty-eight of the entire group were treated on the private service.

The figure of 20.5 per cent to which Dr. Pemberton referred is based upon the sixty-eight cases available for five-year study. Twenty and five-tenths per cent of these are living and have no evidence of recurrence of their carcinoma at present.

Dr. Schumann mentioned the endosalpingioma described by Barzilai. Those tumors that we have classified as of low grade malignancy would probably be included in that group.

Radical surgery, when it can be done completely and safely, is undoubtedly the best treatment for the patient with carcinoma of the ovary. There is only one survivor in our group with actively malignant tumors where the growth was not completely removed. That patient received postoperative x-ray therapy and has remained well and free from any evidence of carcinoma for ten years. All others who have survived for five or more years had tumors that were either completely removable or of low grade malignancy.

In our experience, x-ray therapy has been a valuable adjunct in the treatment of these patients. It frequently prolongs life, but seldom is responsible for complete survival.

ADVANCED ECTOPIC PREGNANCY

With a Report of Three Cases*

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THE great majority of ectopic pregnancies occur within some portion of the Fallopian tube. After a relatively short period of development, their usual fate is either tubal abortion or tubal rupture, with death of the ovum and symptoms of varying severity so far as the woman is concerned. Only under very unusual circumstances will the pregnancy continue to develop so far as mid-pregnancy, and still less frequently is it possible for the pregnancy to proceed to term. Schumann cites the very unusual case reported by Conaway in which the pregnancy proceeded to term while still confined within the tube. An interstitial pregnancy on account of its protected location may develop to a considerable extent before it either ruptures or extends into the uterine cavity, becoming a uterointerstitial pregnancy. More often an advanced ectopic pregnancy represents a tuboabdominal, tuboovarian, intraligamentary, or secondary abdominal pregnancy.

Whether a primary abdominal pregnancy is possible has been a much disputed point, but a recent case reported by Studdiford would seem to fulfill the criteria for such a condition.

Inasmuch as advanced ectopic pregnancy, that is, one extending beyond the fifth month, is an infrequent occurrence, no one individual has the opportunity of seeing a large number of cases. An unusually large series is that of Beacham and Beacham comprising twenty cases from the Charity Hospital in New Orleans.

Among the less frequently observed types of advanced ectopic pregnancy are those that develop secondarily between the folds of the broad ligament. In order for such an occurrence to take place, a rather unusual set of circumstances would be necessary. The ovum would first be implanted in the tube on its lower side, that is, adjacent to the mesosalpinx. After a limited period of development, erosion of the tube wall occurs in such a manner as to permit extrusion of the ovum into the space between the folds of the broad ligament on the involved side. Usually such an accident will result in the death of the ovum and the development of a broad ligament hematoma, but if an area of the chorion sufficient for the nutrition of the ovum remains attached to the tube, its further growth may occur. In association with this growth, further chorionic attachments will be acquired on one or both leaves of the broad ligament, the parametrium, or the lateral wall of the uterus. Such a secondary intraligamentous pregnancy may continue to develop for a considerable period of time, and may

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even go to full term. At the same time there is always the possibility of a secondary rupture of the sac containing the pregnancy into the peritoneal cavity. If no rupture occurs or if it is not removed, the ovum will perish and may be retained in situ for an indefinite period, even many years, and eventually possibly result in a lithopedion formation.

Also, among the less frequently encountered types of advanced ectopic pregnancies are those occurring in a rudimentary uterine horn. Such pregnancies are, of course, technically not extrauterine pregnancies, but are included as the broader term "ectopic," as would be also the rare cervical pregnancy.

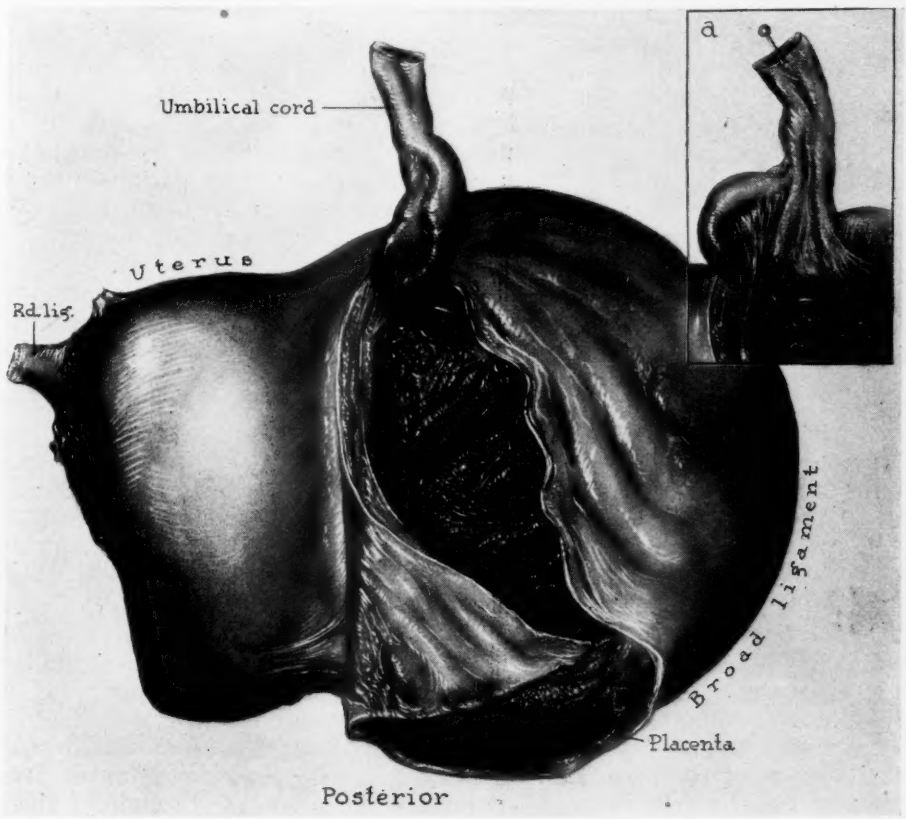

Fig. 1.—The ruptured sac of the full-term broad ligament pregnancy of Case 1. The placenta is still in situ, the rupture being through the posterior wall of the broad ligament. Note in inset the velamentous insertion of the cord, indicating the original site of implantation of the ovum.

How far a pregnancy in a rudimentary horn will proceed will, of course, depend on the size of the horn and the degree of hypertrophy of which it is capable. In our material of 195 various types of ectopic pregnancies, three can be classified as being in the advanced group, two were of the intraligamentary type, and one was a pregnancy occurring in a rudimentary horn.

CASE 1.—M. de H., No. 223668, aged 25 years, white, para i. The patient had had one full-term spontaneous delivery five years previously, and one miscarriage in 1941. Otherwise her past history was irrelevant. In her present pregnancy, she was first seen in the O.P.D. on Oct. 4, 1944. Her last menstrual

period had occurred on March 8, 1944, and the estimated date of confinement was Dec. 15, 1944. No history of any unusual events in connection with the pregnancy was elicited at this time and she was registered as a normal pregnancy of about seven months' duration, the fundus being described as four finger-breadths above the umbilicus.

A month later she was admitted to the hospital with the complaint of intermittent abdominal pain, only moderately severe, with no bleeding. The symptoms subsided in a couple of days and she was discharged as representing a supposed threatened premature labor. No fetal heart sounds were heard, but x-ray revealed a normal near-term fetus presenting by the vertex with no overlapping of the skull bones.

She was readmitted on Nov. 24, 1944, after an attack of very severe abdominal pain. On admission the general condition was good, blood pressure, 128/90; temperature, 37° C.; pulse, 100; red blood cells, 3,390,000; white blood cells, 8,950; hemoglobin, 10.5 grams. She complained of intense abdominal pain. There was some abdominal distention and rather marked tenderness, especially on the right, and the fetal parts were outlined with unusual ease. Fetal heart sounds were readily heard. Examination under anesthesia revealed the fetal head at the level of the spines with an apparently very thin layer of tissue covering it, while the cervix was discovered high up at the upper level of the symphysis. It was of soft consistency and closed. At the previous examination in O.P.D. and at the previous admission the cervix was in its normal location. There was no bleeding. The most probable diagnosis appeared to be sacculation of the uterus with rupture, though some consideration was given to the possibility of an advanced ectopic pregnancy. Operation was undertaken at once. On opening the abdomen, a living near-term fetus was first encountered and was easily extracted. Amniotic fluid was present in the peritoneal cavity, but there was no free blood. Exploration of the pelvis revealed a uterus enlarged to about the size of a three and one-half months' pregnancy lying somewhat to the left of the midline. To the right of this was the sac which contained the pregnancy, and this was identified as the distorted right broad ligament. In its posterior leaf was a jagged rent about 12 cm. in length representing the rupture through which the fetus had escaped (Fig. 1).

The placenta, about the usual size of a full-term placenta, was found attached to the anterior sheath of the broad ligament and to the right of the lateral wall of the uterus. There was no evidence of placental separation. The right ovary appeared normal, while the right tube which presented an open fimbriated end was found to be intact for a distance of about 6 cm., at which point it entered the sac of the pregnancy. Obviously under the circumstances present, no attempt could safely be made to remove the placenta. Repair of the rent leaving the placenta in situ to undergo resorption was considered, but unfortunately, during our manipulations in the exploration of the pelvis, the anterior sheath of the sac was torn, and this resulted in such severe bleeding that the only logical procedure appeared to be to remove the sac together with the uterus as rapidly as possible. This was accordingly done, the uterus being amputated supravaginally and both appendages retained. Removal of the uterus was necessary on account of the attachment of the placenta to its right lateral wall. A transfusion of 1000 c.c. of whole blood was begun during the operation. Her convalescence was uneventful. The baby weighed 2,790 Gm. and did well. The head showed some pressure asymmetry which did not disappear for several weeks. Close questioning after the operation brought out a significant item of history. A little over two weeks after her menstrual period in March, she had an episode of sudden sharp right lower quadrant pain associated with slight vaginal bleeding. A similar but less severe attack occurred in May. This additional history permits a reasonable reconstruction of the course of events. It

seems probable that this pregnancy began as one in the isthmic portion of the tube. Partial rupture probably occurred at the time of her first attack of pain and bleeding, and possibly further rupture between the folds of the broad ligament occurred at the time of her second attack in May. Further evidence as to the original site of implantation is to be found in the presence of a velamentous insertion of the cord at this point.

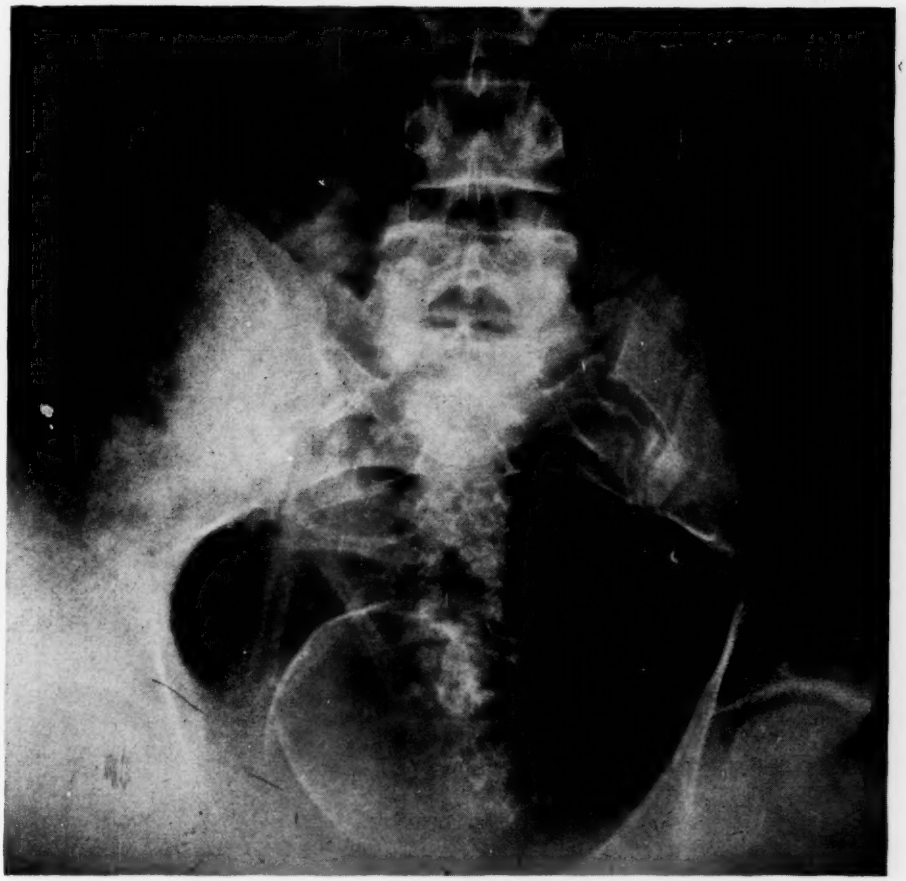

Fig. 2.—Preoperative x-ray showing dead fetus in Case 2.

CASE 2.—M. H., No. 19107, aged 26 years. The patient's past history was irrelevant. In her present pregnancy, the last menstrual period had occurred on Jan. 1, 1945, the expected date of confinement being Oct. 8, 1945. Fetal movements were first noticed in April. Up to May, 1945, the pregnancy was quite uneventful, but at that time an episode of slight vaginal bleeding and abdominal cramps occurred which subsided after rest in bed. Her doctor took her to another hospital in late July, 1945, on account of some vaginal bleeding but with no pain. An x-ray at that time showed a fetal skeleton of about six months. No fetal movements had been noted for a week previous. The fetal heart sounds were not heard. A diagnosis of threatened abortion was made. Six months later, in late January, 1946, her doctor readmitted her to the same hospital for twenty-four hours' observation with a diagnosis of false labor. In May, 1946, an x-ray showed definite evidence of a dead fetus. Menstruation

was re-established in October, 1945. and continued regularly and normally from that time on. She was admitted to Strong Memorial Hospital on Nov. 20, 1946, after having just finished a menstrual period. The time of admission represented twenty-three months after the probable beginning of the pregnancy, and seventeen months after the probable death of the fetus. From September, 1945, to October. 1946, she gained in weight from 157 pounds to 187 pounds.

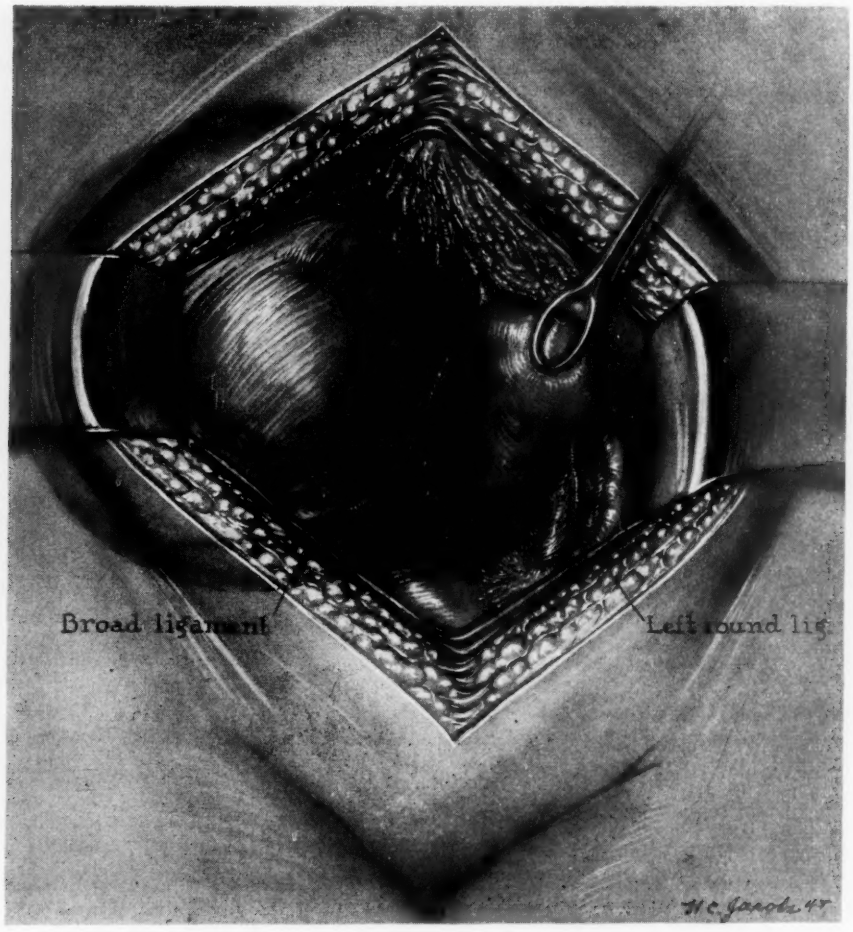

Fig. 3.—The right broad ligament pregnancy in Case 2 after the abdomen was opened.

Examination on admission showed the following pertinent facts: blood pressure, 115/75; temperature, 37; pulse, 72; red blood cells, 4,950,000; white blood cells, 6,600; hemoglobin, 14.0 grams. A mass was felt rising from the pelvis and extending up to the level of the umbilicus. This was rather soft in consistency, nonsensitive, and no fetal parts could be outlined and no fetal heart sounds heard. The Friedman test was negative, and x-ray revealed an obviously dead fetus of about five months' development (Fig. 2).

Pelvic examination revealed the following findings: Outlet: Nulliparous, healthy, no bleeding. Cervix: Small, firm, closed. Uterus: Normal size and displaced posteriorly and to the left. Appendages: On the right was a rather soft mass about 18 cm. in diameter corresponding to the mass felt on abdominal examination. Left appendages were not outlined.

Diagnosis: Extrauterine pregnancy of about five months, with dead fetus.

Operation: A curettage was done in order to obtain some endometrium for study. Laparotomy was then proceeded with. On opening the abdomen no old or recent blood was found in the peritoneum, but a few adhesions were encountered on the right side and were released. The pregnancy was found to be between the folds of the right broad ligament, and the right tube was observed coursing over it (Fig. 3).

Fig. 4.—The mumified but not calcified fetus removed from Case 2.

While freeing adhesions the posterior leaf of the sac was broken open. The mumified fetus was extracted, and the fibrosed placenta was easily peeled off and removed. There was no bleeding. The right tube and some redundant broad ligament tissue were removed, the right ovary being retained and attached near the uterine cornu. The left appendages were quite normal and were retained. Closure of the pelvic and abdominal wounds was completed, silk sutures being used throughout. Her convalescence was uneventful. The mumified fetus weighed 375 Gm. Its crown-rump length was 16.5 cm., the over-all length 32 cm. (See Fig. 4).

The placenta was a well-defined organ measuring 7 by 9 cm., but microscopically the tissue was found to be markedly hyalinized and degenerated with occasional shadow villi to be identified (Fig. 5).

It contained some calcium deposits and numerous phagocytes. Microscopic examination of the tube removed showed chronic salpingitis. The curettings showed early interval endometrium (Fig. 6).

It is interesting to note that no evidence of breast activity was noted postoperatively. One can only speculate as to the time that rupture of the preg-

nancy into the broad ligament occurred. Careful questioning brought out no history of pain or bleeding prior to the fifth month, yet it seems unlikely that rupture occurred at that time with the minimal symptoms she then presented, and considering the degree of development of the pregnancy at that time. This represents, too, a situation in which it would seem perfectly possible for a uterine pregnancy to have occurred in conjunction with the other after menstruation had been re-established.

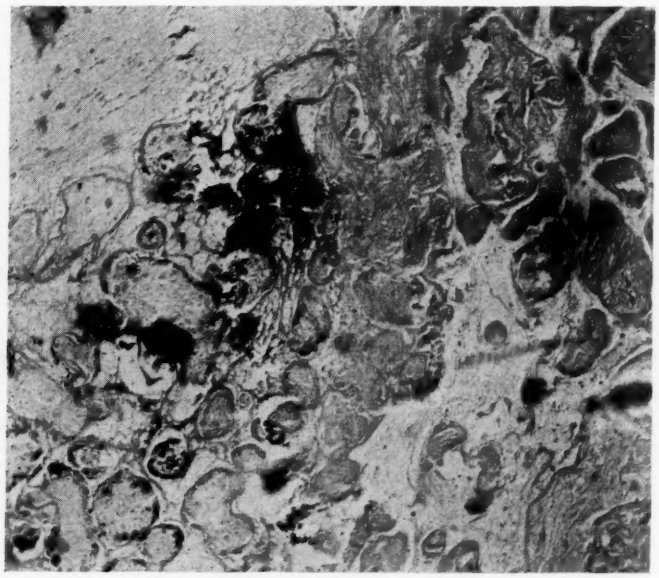

Fig. 5.—Hyalinized placental villi with some calcium deposits from Case 2.

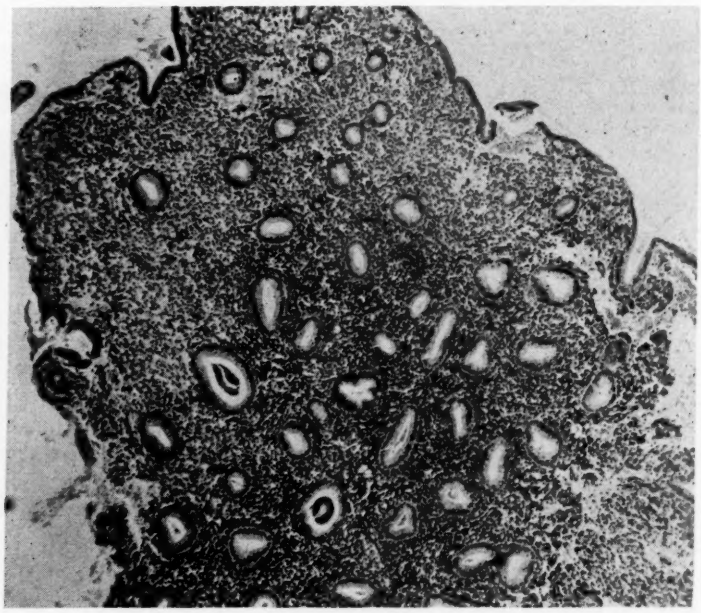

Fig. 6.—The normal postmenstrual curettings obtained from Case 2.

CASE 3.—R. D., No. 247708, aged 18 years. Her past history was irrelevant.

Present Pregnancy.—She was first seen in O.P.D. on May 8, 1946. Her last menstrual period occurred on Nov. 4, 1945, with a scanty two-day flow on Dec. 4, 1945. Her expected date of confinement thus was either Aug. 11, 1946, or Sept. 11, 1946. Examination revealed a mass rising from the pelvis and extending up to the umbilicus. It was described as being rather firmer and less globular than the normal pregnant uterus. No other findings of significance were discovered, and the situation was regarded as a normal pregnancy of between

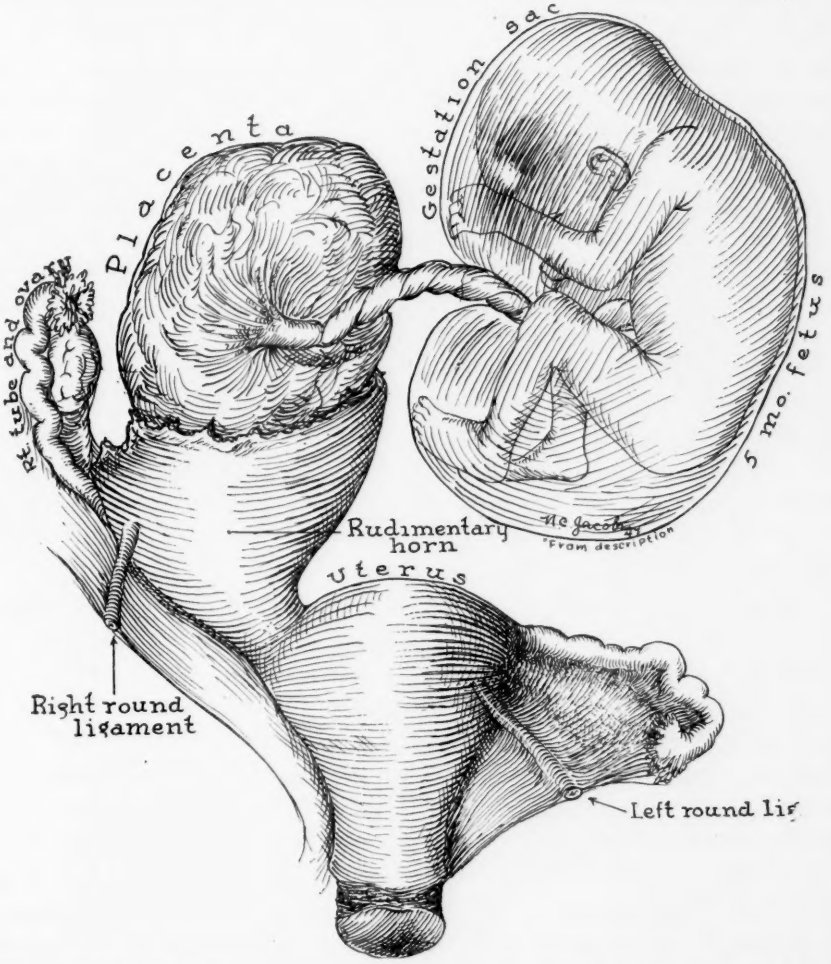

Fig. 7.—Diagram of the findings at operation in Case 3, with complete rupture of the rudimentary uterine born on the right.

five and six months' duration. She was admitted to the hospital ten days later with the complaint of crampy lower abdominal pain and vomiting, but no bleeding. Admission temperature, 36.9° C.; blood pressure, 112/65; red blood cells, 3,100,000; hemoglobin, 12 Gm.; white blood cells, 10,500. There were paraumbilical pain and dysuria with frequency. The urine showed a trace of albumin, and the sediment was loaded with white blood cells and epithelial cells. The uterus could not be differentiated from the mass felt on abdominal palpation. X-ray examination showed a normal fetus of from five to six months' development. A tentative diagnosis of pregnancy with associated urinary infec-

tion was made. In a few hours, however, the whole picture changed and she went into profound shock with all the signs of acute internal hemorrhage. Immediate operation was arranged for, a transfusion of whole blood being begun at the time the operation was begun.

On opening the abdomen at least 1,500 c.c. of fresh blood was found in the peritoneal cavity. A fetal sac of between five and six months' gestation was found free in the peritoneal cavity with a portion of the placenta adherent to a jagged wound, about 8 cm. in diameter, which at first sight appeared to be in the fundus of the uterus. Further exploration, however, revealed that the wound was in a rudimentary uterine horn attached to the right side of a slightly enlarged uterus (Fig. 7).

Its pedicle was narrow, only about 2 cm. in diameter. After removal of the fetal sac and placenta no communication between the rudimentary horn and the uterus could be demonstrated. Both appendages appeared quite normal. The pedicle of the rudimentary horn was ligated and cut, the right appendages were dissected free from it and preserved, being attached to the right uterine cornu.

These areas were covered and the abdomen closed. Silk sutures were used throughout. After completing a transfusion of 1,000 c.c., she responded quickly and had an uneventful convalescence. The fetus weighed 600 grams.

Summary and Discussion

Three examples of advanced ectopic pregnancy are presented, two of the intraligamentary type, and one a pregnancy in a rudimentary horn. One of the former went to term and a living child was delivered at operation, while in the second one the fetus died in situ and was retained for seventeen months before operation was carried out. The third case represented an acute rupture of a five to six months' pregnancy in a rudimentary uterine horn. All of the patients made uneventful recoveries after operation.

In all advanced ectopic pregnancies difficult diagnostic problems may arise. Often they may be overlooked simply because they occur so infrequently that the average person is likely to forget they occur at all. When the patient is first seen late in pregnancy, unless the examiner discovers the slightly enlarged uterus at one side of the fetal sac, he is likely to regard the situation as a normal pregnancy on casual examination. Even if the uterus itself is found, it may be mistaken for a subserous myoma attached to the side of the supposed full-term pregnant uterus. Absence of contractions in the large sac is a diagnostic point of value if the pregnancy is extrauterine, while palpation of the round ligaments in symmetrical relationship to an abdominal mass would indicate that the mass is the enlarged uterus. Death of the advanced fetus with retention might on occasion suggest an ovarian tumor, especially when the small uterus is demonstrated apart from the mass. X-ray picture would provide the answer to the problem. The treatment is, of course, always surgical. The operation performed may be a very simple one on occasion; nothing could have been easier, for example, than the operation carried out in our Case 2. On the other hand, the operation may be an extremely difficult and hazardous one. The difficulties and dangers will depend largely on the relationship which the placenta may have acquired in regard to other structures. Secondary rupture of the sac as occasionally occurs may represent an acute surgical emergency with severe intraperitoneal hemorrhage. The mode of handling the placenta at the time of

the operation is of the greatest importance. When the fetus is still living, or if very recently dead at the time of operation, any separation of the placenta even over a small area will probably be attended by profuse and possible uncontrollable hemorrhage. This was vividly demonstrated to us in our Case 1. In this type of case it is usually preferable not to attempt to remove the placenta, but rather to allow it to remain in situ, and eventually it will undergo resorption. In an intraligamentary pregnancy, however, it may be feasible to remove the whole sac containing the placenta, preserving the uterus if possible. When the fetus has been dead for some time the placental circulation will no longer be active, and the placenta can usually be safely separated from its attachments and removed, but, again, if this proves too difficult, it may be left to undergo resorption. Marsupialization of the sac may on occasion be considered, attaching the edges of the sac to the abdominal wound, in which event the placenta may later separate and be extruded through the opening, either complete or in fragments. We have had no experience with the procedure. It would appear to have a very limited application, but might possibly be considered if infection were already present.

References

Beacham, W. D., and Beacham, D. W.: Obst. & Gynec. Survey 1: 777, 1946. (This article also contains an excellent bibliography of the subject, to which the reader is referred.)
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Discussion

DR. HARVEY MATTHEWS, Brooklyn, N. Y.—Dr. Wilson has forcefully called our attention to a very rare but important subject. We have had only four cases in our service at the Long Island College Hospital during the past thirty-five years. This substantiates the fact that advanced ectopic pregnancy (20 weeks or more) is of rare occurrence. In addition to these cases, I have seen in consultation at another hospital one other case of full-term abdominal pregnancy. This baby was delivered at full term weighing 9 pounds, is living and well fifteen years after operation.

Case Report.—Mrs. R. M., Negro, aged 37 years, para 0, gravida 0, admitted to Long Island College Hospital Aug. 11, 1942, on the service of Dr. George W. Phelan, by whose kind permission I am able to report this case. Family, personal, and menstrual history was irrelevant. She did not know when she last menstruated. Present illness began Feb. 27, 1942, when she began to bleed from the vagina, using three to ten napkins a day and accompanied by constant pain over the lower abdomen. The bleeding (''spotting'') continued at irregular intervals through May 28, 1942. The patient, however, continued to work. On June 15, 1942, vaginal bleeding occurred again; and, for the first time, she sought medical advice. Upon examination her physician suspected abdominal pregnancy. On July 15, 1942, the abdomen was x-rayed, and a fetal skeleton outside the uterus was observed. The fetus was apparently alive, lying high up out of the pelvis. On Aug. 11, 1942, because of constant abdominal pain, the physician referred the patient to the Long Island College Hospital with the diagnosis of abdominal pregnancy. Upon admission this diagnosis was confirmed, and shortly following the vaginal examination the patient went into severe shock. The blood pressure was 50/28 and pulse 152, thready, and weak. After treatment with morphine, plasma, blood transfusion, etc., the patient was operated upon under local 1 per cent novocain, supplemented with gas-oxygen anesthesia. Upon opening the abdomen a seven months' living infant, lying free in the abdominal cavity—the sac having been ruptured presumably by the examination—was easily extracted. The placenta was found to have separated from its attachment to the

posterior surface of the right broad ligament, except at one area along the outer border where it was still lightly attached. The placenta was removed without difficulty, and there was no fresh bleeding. One and one-half liters of free blood were siphoned off, and on further inspection there was some fresh bleeding from the area along the outer border of the right broad ligament. This segment was clamped, cut, and ligated, after which there was no further bleeding. The abdomen was closed with through-and-through heavy black silk sutures, the skin with clips. The infant, a male about thirty weeks old, weighed 1,120 Gm. and died forty minutes after delivery, having breathed only a few times during this interval. At the completion of the operation a second transfusion was given. Convalescence was uneventful, and she left the hospital Aug. 27, 1942, sixteen days after operation.

Dr. Wilson has called your attention to the importance of history. I can only emphasize this point and say it is most important. After a complete physical examination a flat anteroposterior x-ray film will usually clinch the diagnosis. If the nonpregnant uterus can be palpated, or if the fetus is dead, as shown by the x-ray, hysterogram would prove extrauterine gestation. The Aschheim-Zondek or Friedman test is of unquestionable value.

As to the time of operation, we believe that the operation should be performed as soon as the diagnosis is made, except where the diagnosis is not made until late in pregnancy and there is a question of a viable fetus. In such an instance operation may be deferred until the thirty-sixth or thirty-eighth week, provided the patient is kept under constant observation, preferably in the hospital.

The management of the placenta is most important. Realizing, as pointed out by Wharton, that the life cycle of an abdominal or advanced ectopic pregnancy is abnormal, and that the placenta with its "trophoblastic activity becomes attached to and attacks any structure with which it comes in contact," it would seem wise to leave the placenta in situ, after ligating and cutting the cord flush with the fetal surface. The abdomen is closed without drainage. It requires very little "tugging or inspection" to start uncontrollable hemorrhage. Besides, there is little or no danger in leaving the placenta "where you find it." Of course, if there is a distinct pedicle to the placental attachment which may obviously be securely ligated, or where the fetus has been dead long enough to allow of complete "death of placenta," it may be removed without fear of bleeding. In the presence of frank infection the placenta is left in situ and drainage should be instituted through the lower end of the abdominal wound. Marsupialization is not recommended, except where there seems no other way out.

In conclusion, we suggest that the maternal morbidity and mortality could be materially lowered by: (1) early diagnosis and prompt operation; and (2) better surgical judgment in the management of the placenta.

DR. ARCHIBALD CAMPBELL, Montreal, Quebec (By Invitation).—Dr. Wilson is to be congratulated on his having saved all the patients in his series, and on obtaining a living child in the only one in which this was possible. I thoroughly agree with Dr. Wilson that we are all inclined to be too casual in our history-taking of the pregnant patient.

Since 1930, there were 224 early, extrauterine pregnancies encountered at the Royal Victoria Hospital, and over the same period, 162 at the Montreal General Hospital, making a total of 386, of which four were late abdominal pregnancies. During the same period, there were 36,480 confinements. From this small series it would therefore seem that ectopic gestation occurs once to every 100 confinements, and that of all extrauterine pregnancies, approximately 1 per cent reach the stage of viability.

Of the four cases at the Royal Victoria Hospital similar to those reported, the fetus was macerated or dead before coming under observation in three of the cases. In one case, the condition being recognized, the late Dr. H. C. Burgess performed a laparotomy, delivering a living baby. In none of the cases was an attempt made to remove the placenta completely, but rather only a part of the redundant tissue. One patient died of septicemia.

No doubt, in a certain number of instances, patients with extrauterine pregnancy, early or late, recover spontaneously either by a process of absorption, mummification, or extrusion of the fetal parts into the vagina, bladder, or rectum. In this connection, the late Dr. H. M.

Little, in 1924, operated upon a patient in the Montreal General Hospital for ruptured early, acute left-sided tubal pregnancy. On exploring the pelvis at the time of operation, he encountered a large mass filling the entire pelvis. On further investigation, he found that the mass was composed largely of fetal bones. Included were the skull, ribs, mandible, and femur. The pathologist reported bilateral extrauterine pregnancy, left recently ruptured early, right —late abdominal pregnancy and estimated these bones to be those of a six months' fetus. Reviewing the patient's history, it emerged that some four years previously, when believed by her physician to be five to six months pregnant, the patient suffered from symptoms which, at the time, were interpreted as threatened miscarriage. These symptoms kept the patient an invalid for some three months, when ultimately they disappeared. Menstruation returned and the episode was forgotten.

The diagnosis of extrauterine pregnancy rests largely on history. On examination, the presence or absence of demonstrable uterine contractions, the ease with which one can identify fetal parts; a highly-placed transverse presentation should more than arouse suspicion. In most cases of late abdominal pregnancy, the cervix is located high in the vaginal vault. It would seem that x-rays do not give conclusive information. I should like to ask Dr. Wilson if he feels that the sedimentation rate might not add considerable information in suspected cases.

The problem of extrauterine gestation is particularly serious from an ecclesiastical standpoint. I should like to ask the essayist a question pertinent to this situation:

If one were to recognize a late abdominal pregnancy, unaccompanied by symptoms, in the event of the child being alive, but of questionable viability, should such a case be treated as an emergency, or would one be justified in postponing operation in the hope that by waiting one might obtain a viable baby?

DR. ALFRED BECK, Brooklyn, N. Y.—My interest in this subject was stimulated by the difficulty which Dr. J. O. Polak and I encountered in handling a case of extrauterine pregnancy. As a result of this difficulty I reviewed the literature very carefully, and subsequently wrote a paper on the subject which was read at the meeting of the American Medical Association in 1919. In this paper it was suggested that the placenta be removed whenever the circulation of the placental site could be easily exposed and controlled. Whenever, on the other hand, the circulation could not be exposed, I suggested that the placenta be left within the abdomen and the abdomen closed without drainage.

Subsequently, two of my associates encountered full-term abdominal pregnancies and treated them thus: the placenta was left within the abdomen and closure made without drainage. Both made good recoveries. In one of them the abdomen was opened several years later and no trace of the placenta could be found. After that I followed the literature carefully and have noted that a fairly large number of cases have been treated by leaving the placenta within the abdomen and closing without drainage. Seldom was it necessary to do a subsequent operation.

From my observation in my early study and subsequent observation of the literature, I wish to condemn the last suggestion of Dr. Wilson, namely, marsupialization. It gives the highest mortality of all methods of treatment. Most of the patients so treated died from peritonitis.

In my study the mortality seemed to be least when the operation was done about two weeks before term. A number of men carried their cases in the hospital sometimes as long as a month in order to reach this optimum period, and then operated. Of course, when such expectant treatment is used, the patient should be in the hospital so that an emergency operation can be done if the sac ruptures.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—There is a phase of this subject of secondary abdominal pregnancy which I feel requires far more study and which the Fellows of this Society may bring to a conclusion by careful observation of their cases. I think none of us has observed these secondarily attached placentas without being astonished at the blood supply of the placental implantation. When one sees the well-established blood supply in the abdominal cavity, one is continually surprised to find this organ, four-fifths of which may be

on the parietal peritoneum, without any decidual reaction, and yet maintain a sufficient blood supply for the maintenance of fetal circulation.

On two occasions I have had the opportunity of removing a biopsy specimen from the placental site. Usually the placenta is firmly adherent, and one hesitates to remove it to obtain the subplacental areas. In these two cases, there was an enormous number of blood vessels but no evidence of decidual reaction at all as one would expect. I believe, however, that this knowledge is still so fragmentary regarding this problem that whenever possible one should observe the placental site in abdominal pregnancy.

DR. SUBODH MITRA, Calcutta, India.—I made some observations on secondary abdominal pregnancy about nine years ago, and reviewing the world literature I found about 411 cases of advanced ectopic pregnancy, to which I have added nine of my own cases. Some of my cases are very interesting. My first patient was 55 years old and she came to me with a history of vaginal bleeding. I found along with cancer of the cervix, a big tumor in the abdomen, which was discovered to be secondary ectopic pregnancy. She had carried this tumor for the last twenty-five years, and subsequently conceived three times, giving birth each time to a normal child. I did not operate upon that patient, the reason being that when she had carried it for twenty-five years, she could as well carry it for the rest of her life.

The second case was important because of advanced abdominal pregnancy occurring twice successively. I was lucky to make the correct diagnosis at the very first consultation, and she was well after operation. About two years later she conceived again and it was also an advanced ectopic. This time she was in one of the district hospitals where, strangely enough, she was operated upon by a doctor who was one of my assistants and who helped me in my operation on this particular patient. The abdomen was opened, a child obtained, but unfortunately the patient died after this second operation.

My third patient was interesting in the sense that she was diagnosed as one of retroverted fixed gravid uterus of five months' duration. The cervix was found pretty high up and the uterus pressing upon the pouch of Douglas. Upon further examination under anesthesia, a ruptured tube was diagnosed and a fetus of four months' duration was removed by laparotomy.

Sometimes it is very difficult to diagnose these cases of secondary abnormal pregnancy. In the literature I find that in about 33 per cent of cases it was not diagnosed at first examination. In the patients where I had difficulty in the diagnosis, some were at term or near term. They were admitted with complaints of acute pain. Questions arose whether it was due to a twisted ovarian tumor, an acute appendix, or a case of accidental hemorrhage. Many cases were diagnosed only after repeated examinations.

There are several important points in making a correct diagnosis, namely, easily palpable fetus by palpation, cervix found high up behind the symphysis pubis, and an indefinite mass in the pouch of Douglas by vaginal examination.

In regard to the management of these cases, I believe the less one interferes with the placenta the better, because it is difficult to remove in most cases. In some, of course, it is easily detachable. As a matter of fact, in one of my cases the placenta was so firmly attached to the sigmoid colon that I had to resect part of the colon. Since then I have decided not to tackle the placenta but to leave it as it is.

DR. WILSON (Closing).—Dr. Campbell mentioned the incidence of advanced ectopic pregnancy. Ours roughly correspond to his. We have had 198 ectopics and three of these were of the advanced type, also there were three ovarian pregnancies.

Regarding the sedimentation rate, that of course is not a specific reaction. It should not differ with ectopic as compared with normal pregnancy unless there has been some hemorrhagic reaction.

With regard to the advisability of operating or not in the advanced cases with living fetuses, personally I would urge immediate operation because of possible secondary rupture, as was true in our first case.

I have had no experience with marsupialization. On the other hand, perhaps it might have a place where the patient already has infection in the sac.

THE INTRAUTERINE PACK IN THE MANAGEMENT OF POSTPARTUM HEMORRHAGE*

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CONTROL of postpartum hemorrhage continues to be one of the highly important problems which are encountered by obstetricians. On the presence of postpartum hemorrhage which has not been controlled by oxytocic drugs or by abdominal and sometimes bimanual uterine massage, the use of the intrauterine iodoform pack or tamponade for many years has been prominent among the active hemostatic measures we have employed.

Deaths Caused by Obstetric Hemorrhage

There has been a striking decrease in the maternal death rate in this country in somewhat more than a decade. This trend is more or less nation-wide. The lowered maternal mortality rate has been caused by sharp reduction in two of the leading causes of maternal deaths; namely, puerperal sepsis and the toxemias. Maternal mortality caused by obstetric hemorrhage, however, has remained practically constant, except for minor fluctuations. For example, vital statistics of the State of Minnesota show that in the year 1934 the maternal deaths from puerperal sepsis, toxemia, and hemorrhage were approximately twenty, eight, and six, respectively, per 10,000 live births. In the year 1940 the number of deaths from sepsis, for the same number of live births, had decreased to nearly five; deaths from toxemias had decreased to a little more than four; but the number of deaths from hemorrhage had not diminished.

No doubt a wider application of the principles of adequate prenatal care, of conservative and aseptic management of labor, and the employment of chemotherapy have been important factors in the lowering of the maternal mortality rate of the toxemias and sepsis. However, these factors, in addition to more advanced obstetric education and an increase in the number of patients hospitalized for obstetric complications, also should have helped lower the incidence of obstetric hemorrhage.

It is not our purpose in this paper to review the whole subject of obstetric hemorrhage. Among the various causes of such hemorrhage, that which occurs post partum is responsible for the largest proportion of maternal deaths from hemorrhage. Analysis of the management in such cases has shown that, although deaths from postpartum hemorrhage are not entirely preventable, under ideal conditions they are almost preventable. Among these ideal conditions are adequate prenatal care, conservative management of labor and its third stage, hemostasis, and the replacement of loss of blood volume.

*Read before the meeting of the American Gynecological Society, Montebello, Quebec, Canada, June 17 to 19, 1947.

Opinion Concerning the Intrauterine Pack

Review of the literature furnishes ample evidence that the employment of the intrauterine pack for postpartum hemorrhage is a controversial subject.

Cosgrove, Leff, and Hunter indicated that the use of such a pack should be kept to a minimum; they asserted that the postpartum use of uterine tamponade is unphysiologic, that it holds open the uterine sinuses, thus allowing loss of blood to continue, and that the uterus then distends rather than contracts, so that a hemorrhage which otherwise would be revealed is converted into a concealed hemorrhage. These writers said that they employ oxytocic agents and other measures, particularly bimanual compression, in the control of the uterine loss of blood, and that they may even maintain this compression for a prolonged period. Sherrick, Davis, and others[1, 14, 16, 19, 21] among the obstetricians who write about the management of postpartum hemorrhage, do not mention the use of intrauterine packs. The use of the hot intrauterine douche as a hemostatic measure, before resort to packing, was advised by Corbet and DuPuy; this procedure seems to enjoy especial favor among British authors. The douche employed is carried out with either hot water or hot dilute acetic acid.

A large number of obstetricians, Pastore and Stander, Falls, DeLee, and others[7, 9, 10, 11, 17, 20, 23] have said that intrauterine tamponade should be used as soon as it becomes evident that postpartum uterine hemorrhage is not being controlled by the usual available measures. These authors asserted that the intrauterine pack acts in two ways to control the bleeding; (1) by actual tamponade, and (2) by serving as a foreign body to stimulate uterine contraction. The authors referred to were in general agreement that, when packing becomes necessary, it should be done without delay.

The type of pack used varies, and many writers have said that this is of great importance. Falls, in 1937, used a pack moistened with a 1 per cent solution of cresol (lysol); DeLee in 1938 recommended use of a pack moistened with an 0.5 per cent solution of cresol (lysol); Soule used plain, iodoform, or sulfanilamide gauze packs. Randall remarked that it is not important to argue about the type of pack to be used, but that it is important, after the decision to pack has been reached, to do it quickly and correctly.

The Present Study

Third Stage of Labor.—We wish to outline briefly the management, in general, of the third or placental expulsion stage of labor which we have followed. This procedure has varied somewhat in the course of nearly thirty years.

Before proceeding with a description of the management of the third stage of labor we should like to mention administration of the extract of the posterior lobe of the pituitary gland as the second stage ends. We have almost never used this extract in the course of labor. The exact time of injection has varied from time to time; usually the extract has been injected directly after delivery of the baby's head or shoulders or entire body. For two years it was the practice to inject the extract immediately after expulsion of the placenta. However, for the greater part of this period it has been customary to inject intramuscularly 1.0 c.c. of alpha-hypophamine (pitocin) during delivery of the head and shoulders of the baby.

Because of the controversial nature of this subject, we feel we should state that in our management of the third stage of labor, we have been mindful of the mechanism of placental separation and expulsion. Also, it may be stated

that we have followed with reasonable uniformity the rule of withholding massage of the uterus until symptoms indicate that placental separation has occurred. When evidence of separation of the placenta is present, and the placenta has not been expelled spontaneously, or if copious bleeding occurs, the placenta is delivered by simple expression. If the placenta is retained without signs of separation for more than twenty minutes, or if bleeding persists, an attempt is made to deliver the placenta by the Credé maneuver. Failure of this attempt calls for a rest of at least five minutes to permit relaxation and perhaps separation of the placenta, after which the Credé maneuver is repeated at intervals of, perhaps, ten minutes, for approximately an hour post partum. Delivery of a retained placenta by the Credé maneuver is facilitated, in some instances, by sufficient anesthetization of the patient to relax the uterus. In case the placenta has not been delivered within an hour, or in case bleeding requires interference before this time has elapsed, the patient is anesthetized and the placenta is delivered manually.

After delivery of the placenta, an atonic uterus or persistent bleeding indicates the need for vigorous massage of the uterine fundus and, usually, for the intramuscular or preferably intravenous administration of an additional oxytocic agent in the form of an active aseptic ergot preparation.

Indications for Intrauterine Packing

If bleeding continues to be excessive in spite of the treatment we have outlined, the uterus is packed firmly with sterile gauze. Packing is most imperative when the uterus exhibits a continuing tendency to relax. Special instruments for packing have been tried and abandoned. The most effective results are obtained when packing is carried out as follows. Two fingers are inserted in the uterus, with the palm of the hand anterior. The gauze is carried along the fingers with a blunt-nose packing forceps or placental forceps or, in some instances, with the first and second fingers of the other hand. Washed iodoform gauze 2 inches (5 cm.) wide in 5 yard (4.6 m.) lengths is employed, and several lengths are tied together when more packing is necessary to fill the uterus completely. In cases of severe bleeding from an atonic uterus, the vagina also is packed tightly. When the delivery has been complicated by placenta previa, uterine and vaginal packs usually are placed as a precautionary measure, even though bleeding is not pronounced.

Uterine tamponade has been employed in certain cases of postpartum hemorrhage on the obstetric service at the Mayo Clinic since 1918. The procedure is carried out without undue delay as a hemostatic measure in cases in which postpartum bleeding is not readily controlled by oxytocic agents and uterine massage. From January 1, 1918, to December 31, 1945, there have been approximately 12,000 deliveries, and in the course of this period uterine tamponade has been done 267 times, an incidence of 2.3 per cent.

The indications for the employment of intrauterine tamponade among these 267 patients are summarized in Table I. The uteruses of fifty-six primiparas and fifty multiparas were packed because of persistent uterine hemorrhage after the third stage of labor; in four of these primiparas and in seven of the multiparas clinical signs of shock had developed. The average amount of blood lost through hemorrhage by the primiparas was 690 c.c. The average amount of blood lost in the same way by the multiparas was 620.7 c.c. The low average amount of blood lost for which tamponade was done is perhaps ex-

TABLE I. INDICATIONS FOR INTRAUTERINE PACKING AMONG 267 WOMEN

CONDITION	PRIMIPARAS	MULTIPARAS	COMBINED
Hemorrhage persisting after delivery of placenta	56	50	106
Hemorrhage persisting after manual removal of placenta	21	25	46
Uterus remaining atonic after manual removal of placenta	27	31	58
Uterus remaining atonic after cessation of postpartum bleeding	11	46	57
Total	115	152	267

plained by the prevailing policy of early institution of active hemostasis. After manual removal of retained placentas from twenty-seven primiparas and thirty-one multiparas, hemorrhage occurred for which intrauterine packing was required. Undue relaxation or atony of the uterine musculature often is the cause of postpartum hemorrhage and placental retention. Because this relaxed condition of the uterus may persist after manual removal of the placenta, we believe that in these cases uterine tamponade is a valuable prophylactic measure in the event that firm contraction is not induced promptly by other methods. Intrauterine tamponade was employed for twenty-one primiparas and twenty-five multiparas after manual removal of the placenta although no significant hemorrhage had appeared. Intrauterine packing also was carried out, because of persistent uterine atony after cessation of bleeding, for eleven primiparas and forty-six multiparas. The employment of packing in these cases may be called "prophylactic" or "elective." In each case the postpartum hemorrhage seemed to be controlled, but the uterus remained in an atonic condition, and as a precautionary measure the pack was inserted, before the patient was returned to her bed.

One hundred seventy-five of the 267 patients (sixty-three primiparas and 112 multiparas) had relatively easy deliveries consisting of 139 spontaneous and thirty-six outlet forceps deliveries. The remaining ninety-two patients (fifty-two primiparas and forty multiparas) were delivered by more formidable procedures than outlet forceps. The various deliveries and their number are shown in Table II.

Interesting obstetric abnormalities present in this group of 276 patients are listed in Table III. These abnormalities were chiefly defects of the placenta or placental site, which, when present are likely to be important factors in the

TABLE II. TYPE OF DELIVERY AMONG 267 WOMEN REQUIRING INTRAUTERINE PACKING

DELIVERY, TYPE	PRIMIPARAS	MULTIPARAS	TOTAL
Spontaneous	41	98	139
Outlet forceps	22	14	36
Forceps unqualified	4	1	5
Low forceps	22	8	30
Mid forceps	3	2	5
High forceps		1	1
Breech deliveries (all types)	7	8	15
Version and extraction	1	7	8
Unspecified	7	7	14
Destructive	2		2
Forceps rotation	2		2
Dührssen's and forceps	2		2
Multiple			
Twins	2	5	7
Triplets		1	1
Total	115	152	267

causation of postpartum hemorrhage. There appears to have been a tendency for these abnormalities to occur in multiparas, for in eighteen cases of such abnormalities, fifteen patients were multiparas and only three were primiparas. Three patients had uterine fibromyomas.

TABLE III. ABNORMALITY OF PLACENTA AMONG WOMEN REQUIRING INTRAUTERINE PACKING

	PRIMIPARAS	MULTIPARAS
Partial placenta previa		6
Central placenta previa		2
Complete separation of placenta		1
Premature separation of placenta	1	
Abruptio placenta	2	2
Circumvallate placenta		1
Bilobed placenta		1
Succenturiate lobe of placenta		2
Total	3	15

Persistent Bleeding Despite Intrauterine Packing

Persistent postpartum bleeding ordinarily is controlled by a well-placed intrauterine pack. Six of our patients, three primiparas and three multiparas, continued to bleed through the pack. The bleeding of three of these six patients was controlled effectively by repacking of the uterus. However, the hemorrhage of the remaining three patients could not be controlled by the use of oxytocic agents, massage, or the reinsertion of an intrauterine pack. Hence, abdominal hysterectomy was done.

The first of these three latter patients was a primigravida 31 years old. A uterine fibromyoma was discovered during her prenatal examination. Delivery was spontaneous, after an uneventful pregnancy and labor. Because of repeated postpartum hemorrhages not controlled by any of the usual measures or by snugly placed uterine tampons, subtotal hysterectomy was performed.

The second patient, 37 years old, para iii, gravida iv, had bleeding from a marginal placenta previa. Artificial rupture of the amniotic sac controlled the hemorrhage from the placenta previa, and a normal infant was delivered. Postpartum hemorrhage, however, was uncontrolled, and total abdominal hysterectomy was done.

The third patient, para viii, gravida ix, 36 years old, was delivered spontaneously after unusually rapid first and second stages of labor. The placenta was removed manually because of immediate profuse postpartum hemorrhage. Bleeding continued from an atonic uterus which was firmly packed; 1,000 c.c. of blood was transfused to the patient. The packing was removed after twelve hours; a state of mild shock ensued. The appearance of signs of peritoneal irritation and persistent low blood pressure led to a diagnosis of ruptured uterus, which was confirmed at the time of abdominal hysterectomy. Rupture of the uterus may have been caused when the placenta was removed, or by either the violence of the uterine contractions during the precipitate labor, or by packing of the uterus.

Febrile Morbidity Rates

The morbidity rate among patients whose uteruses have been packed is not high. If the accepted standard for febrile morbidity of 100.4° F. (38° C.) persisting for two successive days exclusive of the first postpartum day is employed, then twenty-nine of the 267 patients are included in the morbidity group. This produces an uncorrected morbidity rate of 10.9 per cent which is lower than the morbidity rate (13.1 per cent) among patients with anemia

after postpartum hemorrhage for which the intrauterine pack was not employed. Hunt reported a series of seventy-seven cases, involving the years 1934 to 1941, in which the intrauterine pack was employed for postpartum hemorrhage; in the last five years of his series the incidence of febrile morbidity was 4.4 per cent among forty-six patients for whom the intrauterine pack was employed.

Apparent causes for the febrile reaction in our series were infection of the breasts, one instance; infection of the urinary tract, ten instances; phlebitis and embolism, two instances; uterine infection, six instances; and undetermined cause, ten instances. If correction is made for those patients who had infection of the breasts or the urinary tract, phlebitis, and embolism, the number of patients who had a febrile postpartum course consequent to packing of the uterus would be sixteen (including those who had febrile reactions of undetermined cause), an incidence of 6 per cent.

Fatality Rate

There was one death. The patient was a para viii, gravida ix, 39 years old, in whom rupture of the amniotic sac occurred forty-eight hours prior to the onset of labor. After several vaginal examinations carried out in the home, the patient was brought to the hospital. She was delivered of triplets after prolonged first and second stages of labor associated with poor uterine contractions. The placenta was retained; after seventy-nine minutes moderate hemorrhage developed. When efforts to deliver the placenta by the Credé maneuver failed, the placenta was removed manually and the uterus was packed. There was postpartum febrile morbidity, and hemolytic streptococci were found in the uterus. The patient died on the eighth day post partum (this death occurred prior to the advent of the chemotherapeutic agents). Incidentally, no death from hemorrhage occurred in the ten years prior to the time of this report in more than 7,000 deliveries.

Summary and Conclusions

Since 1918, we have employed the intrauterine iodoform pack as a hemostatic agent in certain instances of persistent postpartum hemorrhage. This method of hemostasis has given excellent results when it has been carried out aseptically before the loss of blood became severe.

The chief indications for uterine tamponade are persistent postpartum hemorrhage from an atonic uterus or from the placental site, shock, and manual removal of the placenta.

The morbidity rate of the series of patients for whom uterine tamponade was done was not unduly high (10.9 per cent). In comparison, the morbidity rate among patients who were anemic as a result of postpartum hemorrhage and whose uteruses were not packed was 13.1 per cent. The one death in the series presents convincing evidence of the danger of carrying out obstetric procedures through a contaminated birth canal. Perhaps, if such a patient were admitted to the obstetric service today, the use of penicillin or chemotherapy might alter the outcome.

One of us (R.D.M.) has employed the intrauterine iodoform pack for more than thirty years. In that period, only one patient has exhibited sensitivity to iodine. The reaction consisted of slight generalized erythema which appeared after two successive deliveries in which an intrauterine pack of iodoform gauze had been employed. The first episode was thought to be a reaction to barbit-

urates, but, after the rash had appeared for a second time, it was attributed to sensitivity to iodine.

Available evidence indicates that the employment of the intrauterine pack to assist in control of persistent postpartum hemorrhage has a definite place in the management of this condition.

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Discussion

DR. ALEXANDER M. CAMPBELL, Grand Rapids, Mich.—There are a number of arguments against uterine tamponade in the management of postpartum hemorrhage, some of which are as follows: (1) that it is a nonphysiologic procedure; (2) that it is rarely, if ever, necessary if labor is properly managed, particularly in the third stage; (3) that there is too much danger of infection; (4) that it will not always stop the hemorrhage; (5) that one may pack a uterus that has been ruptured and that packing may actually produce a rupture.

If hemorrhage could always be prevented when it occurs during maternity, obstetrics would soon become a most popular and provocative specialty. The fear of fatal bleeding hangs over the accoucheur's head like the "sword of Damocles," for he never knows when it will occur nor how small an amount of blood will be disastrous.

We believe that more pregnant women die from hemorrhage than from any other cause and, as Dr. Mussey has stated, the majority of such deaths are due to postpartum hemorrhage. Of the three great messengers of death in maternity, hemorrhage plays the most important and dramatic role.

We would like to believe that it is never necessary to pack a uterus, but until the standard of care of the parturient woman is considerably improved, this consummation will probably never be achieved.

In my official capacity as maternal health consultant in the State of Michigan, we are chiefly concerned with maternal care as it is conducted in rural areas and in small hospitals where it is impossible to immediately replace dangerous blood loss. We are seriously concerned when a woman bleeds to death from postpartum hemorrhage, but we submit that frequently there is not sufficient concern over the woman who does not die but who sustains mass hemorrhage which invites infection, delays her convalescence, interferes with

her nursing her baby, and robs her of a high level of health and happiness which she deserves, and burdens her with several months of invalidism.

During the last ten years we have been advising that a simple sterile uterine packing unit be placed in every delivery room, so that, when a postpartum hemorrhage occurs that cannot be controlled by the well-known methods suggested by Dr. Mussey, it can be stopped immediately and without delay by properly packing the uterus. This will almost invariably arrest the bleeding. We believe that in the smaller hospitals at least, it is better and easier to prevent blood loss than to replace blood loss when it cannot be done immediately. Dr. Mussey states that in the Mayo Clinic the incidence of uterine packing is once in about 430 times. We know of other hospitals where it occurs once in 150 times. Dr. Davis informs us that in the Chicago Lying-in Hospital where the routine administration of ergotrate intravenously is done while the child is being born, the incidence of uterine packing has almost reached a vanishing point.

Concerning the various chemicals and antibiotics that have been and are being used in the pack, we wish to state that through the courtesy of Johnson and Johnson Research Department, because of our interest in uterine tamponade, we have been presented with six dozen packages of gauze impregnated with crystalline potassium penicillin, chemically sterilized and hermetically sealed in glass containers. This pack will remain sterile for an indefinite period, which is important. We are placing these packs in a few hospitals in our State for experimental study.

We believe that further progress will be made toward improving the efficiency and safety of the uterine pack.

Absorbable oxidized gauze is being used to control hemorrhage in general surgery and this or some other preparation may become of practical value in controlling postpartum hemorrhage.

In conclusion, we suggest (1) greater care must be exerted to control postpartum hemorrhage; (2) uterine tamponade carefully and efficiently performed without delay is often a lifesaving measure; (3) it is better in some environments to prevent loss of blood by packing the uterus, than to attempt to replace blood loss where blood transfusion is not immediately available. Further research work is necessary to increase the efficiency and safety of this procedure. We look forward to the time when hemorrhage, and especially postpartum hemorrhage, will play a much more minor role in maternal mortality than it does today, but for the present we submit that while a uterine pack should rarely be necessary, it should always be available, in the delivery room of every hospital.

DR. SAMUEL A. COSGROVE, Jersey City, N. J.—I would interpolate here that the situation detailed by Dr. Campbell is quite foreign to the consideration of this matter as it pertains to great clinics like Dr. Mussey's and others which are well organized to combat hemorrhage. And I would not at all quarrel with what he pointed out, in what I am about to say now.

The essayists have pointed out a lag in the improvement of statistics in puerperal deaths from hemorrhage, implying perhaps that further improvement in that regard might be attained by a wider appreciation, and a more frequent use, of a number of measures, among them that of the intrauterine pack. While our own management of the third stage of labor currently differs in detail from that sketched in the paper, I would entirely concur with the author in the great importance of that management in the prophylaxis of postpartum hemorrhage. Indeed, I would almost feel that the conduct of that stage constitutes the primary responsibility of the obstetrician, and that he had better delegate the actual delivery of the baby to a subordinate, rather than this responsibility.

In the management of the hemorrhage itself, the authors esteem the intrauterine pack as a prominent and valuable hemostatic measure, so much so that they actually employ it rather extensively in prophylaxis against potential bleeding. But they do admit that in some cases it has failed to control bleeding. In our clinics we would exactly reverse this emphasis. We believe that it fails to control bleeding not responding to other measures and is unnecessary in those cases which do.

They say that uterine pasking was used 267 times in their hands in 11,651 deliveries, an incidence of 2.3 per cent. Had the same ratio been applied to the 8,400 cases delivered by us in 1946 alone, we would have used it 193 times. We did not, in fact, use it in a single case, but we lost no cases in that time from postpartum hemorrhage. Our failure to use the intrauterine pack, therefore, cannot be assigned as a cause of increased mortality from postpartum hemorrhage.

Moreover, in reviewing such deaths, both in our own earlier experience, and from published reports from other clinics, as well as from information gained by personal observation and communications from other sources, a majority of the fatalities due to postpartum hemorrhage *were* subjected to packing. This would seem to indicate the futility of the packing in at least the worst cases of inertia. Besides its futility, its use has been time consuming when time is precious, has sometimes concealed significant continuing hemorrhage, and has more than possibly concealed more or less obscure pathology causing bleeding, which has been mistakenly attributed to inertia. This would actually appear to have been possible in the essayist's third case of hysterectomy.

The essayists' use of tamponade in a large series of cases in none of which the average blood loss exceeded 690 c.c., and in 57 of which it was employed after bleeding had ceased, and in 47 of which *bleeding never had occurred at all,* would seem poor evidence of the necessity of this procedure in *any* case, and certainly does not constitute proof that it contributes to the lowering of hemorrhagic mortality.

I, therefore, cannot refrain from reiterating my belief that: uterine tamponade for postpartum hemorrhage is unphysiologic because it directly circumvents the effort otherwise made to empty completely the uterine cavity, reduce that cavity to the smallest size possible and the bulk of the myometrium to the smallest mass possible; that it is unnecessary in the less severe cases and futile in the more severe ones; that it may actually militate against the patient by loss of time in resorting to more definitive surgical measures; by obscuring accurate diagnosis; and by hiding continuing significant hemorrhage.

DR. GERALD C. MELHADO, Montreal, Canada.—The frequency and severity of postpartum hemorrhage bears a definite relation to the management of the third stage of labor. That this incidence shows no appreciable decrease, but is in fact increasing, may be verified by a careful analysis of records in almost any clinic.

One reason for this increase is undoubtedly due to more rigid criteria as to what constitutes hemorrhage. Some years ago most clinics were satisfied to estimate the blood lost, but in recent years the measured amount of blood and the hemoglobin determination are the deciding factors.

In our clinic at the Royal Victoria Maternity Hospital a blood loss of 500 c.c. or more and a hemoglobin below 70% is classified as a postpartum hemorrhage. Severe blood loss does not always seriously jeopardize the patient's life while, on the other hand, a loss of less than 800 c.c. has resulted in death.

A factor of no small importance, therefore, is directly related to the proper prenatal care of anemic states. It is also well to remember that blood loss bears some relation to size of the baby, placenta, and is influenced by anesthesia and the duration of labor.

Knowledge of the mechanism of placental separation must be kept in mind if undue hemorrhage is to be avoided, whether one accepts the older idea of separation by means of a retroplacental hematoma, or the more modern view of a decrease in size of the uterine cavity and area of placental attachment leading to a partial and finally complete separation. In the modern view as the uterus contracts and retracts its walls become thicker and thicker and the area of placental attachment smaller, so that eventually the compact placental can no longer follow the changes and is consequently separated from the uterine wall.

We are, therefore, of the opinion that no attempt should be made to hasten this process by massage of the uterus, or to endeavor to express the placenta before separation has occurred; for this endeavor to hasten placental separation is a basic factor in many instances of postpartum hemorrhage.

The author has described his method of the management of the third stage of labor and while methods of management vary in some respects, the fundamentals remain the same in all clinics—whether oxytocics should be given during the expulsion of the child immediately following or only after the placenta has separated and been expelled is mostly a matter of individual experience. There are, however, many instances of retained placenta following the use of pituitary extract administered before the separation of the placenta has occurred. We have tried all methods and at the present time are administering an oxytocic after the placenta has been expressed, the oxytocic used being ergometrine intravenously or intramuscularly. The only exception to this rule of awaiting placental separation is in the presence of excessive bleeding, when our method of management is similar to the author's, i.e., attempts are made to separate and express the placenta by means of a Credé maneuver. If this fails and bleeding persists, manual removal is done, associated with or followed by the administration of intravenous ergometrine, plasma, and blood, and the uterus is immediately packed. With respect to packing of the uterus, it seems to me that arguments against it are not valid. The fear of infection is exaggerated and has in the past been overemphasized. It is not the entrance of a pack into the uterus that is the factor behind infection, but rather the loss of blood. Neither is the type of pack of too great importance —whether wet or dry, and if wet whether this or that antiseptic is used. What is more important is that when packing is necessary it should be done early, promptly, and thoroughly. The amount of gauze used should be just sufficient to cause the uterus to contract firmly—about 5 yards. To overpack the uterus will defeat the purpose of a pack by distending the uterus and, so partially paralyzing it, resulting in more bleeding.

If an intra-uterine pack fails to control bleeding it is nearly always the result of overdistention of the uterus by too large a pack, except in cases of neoplasm, or placenta accreta. It is therefore wiser to "underpack" rather than "overpack" the uterus.

In most instances when packing is necessary it is also wise to pack the vagina. With the discovery of "*Oxycel,*" we may have an agent of great value for the control of hemorrhage, but at present the strips of material are too small to be efficiently useable in an emergency. I have been given to understand that Oxycel in strips of 1 yard long and 2 inches wide will soon be obtainable.

Between the years of 1940 and 1946 on the old standard of determining postpartum hemorrhage, we had approximately 112 cases, but under the new classification of 500 c.c. or more and with the hemoglobin dropping below 70 per cent, there were 674 cases.

In spite of this apparent increase in postpartum hemorrhage, the mortality is considerably less because of the use of plasma, blood, and prompt intrauterine packing. In fact, during this latter period there was one death in 338 cases of postpartum hemorrhage. This death could have been avoided if the gravity of the patient's condition had been recognized and the uterus promptly packed; because she rallied for a time from her severe blood loss, but the subsequent so-called slight bleeding was sufficient to result in death, in spite of 3,500 c.c. of plasma and blood.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—I am not sure it is wise to prolong this discussion indefinitely as to opinions in regard to the use of the intrauterine pack, but I cannot refrain from saying a word for it, particularly in its relationship to teaching young students and medical practitioners. I feel that there is certainly ample ground for us to cling to that teaching of this subject. Naturally, a pack in the uterus in its attached position interferes with the contractility of the organ. And yet it is a stimulus, or so it seems to us, to uterine contraction. Again I think it is important in the postdelivery phase of placenta previa. We lose our cases with hemorrhage after delivery as well as before delivery unless we prevent hemorrhage, take careful provisions to do so by pack or by insurance that there is no bleeding from the lower uterine segment where it is likely to occur. Unless this is done there will be continued deaths from so-called antepartum hemorrhage which causes death in the postpartum period.

Again, I doubt if oxytocic agents are safe for the instruction of medical students and interns. Even trained obstetricians have delivered the first fetus and found that there

was a second fetus contained in the uterine body. If we teach the use of oxytocics we run the danger that our students and interns may overlook that possibility and have trouble.

Again, in the cases where there is difficulty in the delivery of the aftercoming shoulder and the baby's body, I think danger is incurred with the administration of ergot immediately after the birth of the head. One of my men has been trying this and encouraging me to employ it, but I think that in the third stage oxytocic agents should not be used.

Personally, we use the intrauterine pack very frequently. I think our results have been increasingly better with cases of postpartum hemorrhage, but of course the best improvements have come with the blood bank and the plasma. In the large hospital practice I think this is due to the great availability of the intravenous fluids and blood.

DR. JOSEPH L. BAER, Chicago, Ill.—I think it best to limit my remarks to the experience that we have had at the Michael Reese Hospital where we went through the phases of the hot douche, the one-hour holding of the fundus uteri after delivery and the frequent use of the pack to the more recent techniques. We adopted the ergotrate intravenous procedure as soon as it was proposed. We use it immediately upon the stemming of the shoulder under the symphysis. We have yet to encounter the theoretical risk of locking a second fetus. The frequency of the use of the pack has dwindled with us almost to the vanishing point. I am in complete accord with Dr. Cosgrove's analysis on that position: that, used when there is little hemorrhage it is superfluous; used when there is a pathologic condition, when the uterus is prevented from controlling its own bleeding, it is futile.

The experience of the accoucheur plays a very important role in the interpretation of what constitutes postpartum hemorrhage. If a man has had an unhappy experience with perhaps a fatal hemorrhage, he is quite prone to look upon the next instance of bleeding with a considerable degree of anxiety and resort to immediate and vigorous measures of control which may be entirely superfluous. Furthermore, I think employment of the pack is in reverse proportion to the experience of the accoucheur.

I agree again with Dr. Cosgrove who believes that the resident may well be left to the delivery itself, and the third stage supervised by someone more experienced than he.

I think it might be of interest to this group to know that the problem confronting Dr. Campbell in the State of Michigan, which is a problem also confronting the small institutions all over the United States, is by way of being solved to some extent in the next several years, namely by the availabilty of blood. The National Red Cross is preparing to develop a nationwide service in the obtaining and distributing of blood for all indications in which blood transfusion is required and, of course, in that group the maternity patient comes almost first. The American Medical Association has given its approval to this endeavor of the National Red Cross, provided it is carried out on a community level and with the cooperation and consent of the local county medical societies. I am inclined to think that this will in due course make blood available in adequate quantities for many smaller institutions which do not now have this remedy. From the standpoint of the patient in the third stage of labor it is far better to give her a replacement of 500 c.c. than to resort unnecessarily to the intrauterine pack.

DR. VAN BOUWDIJK BASTIAANSE, Amsterdam, Holland.—Regarding hemorrhage in the third stage of labor, in our clinic we rarely observe severe bleeding post partum. I doubt if there has been one patient in our 9,000 deliveries who has been packed in the years 1923 to 1938 in the obstetric department of which I was head before I was appointed head of the department of obstetrics and gynecology of the University of Amsterdam. Of our hospital patients, who had prenatal care, including those patients who had cesarean section for placenta previa, etc., the mortality was less than one in a thousand. In our clinic in Amsterdam we also have very seldom seen bleeding—I cannot give you the figures, but I am sure that we have not used the intrauterine pack more than once a year in about 2,300 deliveries a year.

The reason we have so few cases of hemorrhage, I think, is that we are very conservative. First of all, we teach the students and residents that the placenta will not be pushed out before half an hour after the birth of the child.

Second, regarding the anesthesia, in Holland we very rarely use an anesthetic in a normal delivery. Of course, it is always used in an artificial delivery, in my clinic most times spinal anesthesia. In those cases where it is necessary to have relaxation of the uterus, e.g., in version and extraction, general anesthesia is given. I think if we are fairly conservative in the choice of our anesthesia and think of the possibility of its influence on the uterus, that then the chance of bleeding will be much less. In cesarean section we never pack, and in placenta previa only in a very few cases where it is not possible to stop the bleeding.

DR. ARTHUR H. BILL, Cleveland, Ohio.—If one encounters a well-developed postpartum hemorrhage he will realize that the surest treatment of this condition is prophylaxis. I believe in starting immediately with the birth of the child to stimulate the uterus to contract and prevent loss of blood in the third stage. If the uterus fills up with blood before the placenta is delivered, a considerable loss of blood may be encountered. Shortly after the introduction of pituitrin I inaugurated a plan of giving pituitrin immediately upon the birth of the child, and then giving an ergot preparation immediately upon the separation of the placenta. We have used this procedure for more than thirty years in every case. That means that we have used an oxytocic in about 100,000 cases, and I have not encountered a case of retention which could be attributed to pituitrin. I have however, been reluctant to give ergot until the placenta is ready to be delivered. I prefer pituitrin first, and intravenous ergotrate as soon as the placenta is separated. In my practice I have been through all the various stages from hot douches to the present-day methods, and in the early days of my practice I packed with iodoform gauze very frequently. We had no oxytocics, no pituitrin, no reliable ergot preparation, and no blood transfusion, and did not know what the blood pressure was, for we had no sphygmomanometer. We would pack the uterus with little hesitation, but this was not always successful. Often after packing the fundus was hard and everything seemed satisfactory. A few minutes later the uterus would soften and fill with blood behind the packing. A relaxed uterus cannot really be packed. Again, too much packing keeps the uterus unnaturally distended. Since the routine use of oxytocics we pack less and less. In fact, packing for postpartum hemorrhage is seldom used. Personally I cannot recall having done so for a number of years.

Why is it that the mortality in postpartum hemorrhage is still as high as stated? In our experience one of the most satisfactory things in the progress of obstetrics has been the reduction of postpartum hemorrhage. We see it very rarely. In addition to the routine administration of a pituitary preparation, a hand should be kept on the fundus continuously during the third stage and if relaxation occurs the oxytocics should be repeated. Try to keep the uterus from filling up with blood before the placenta is expelled, for loss of blood predisposes to more loss of blood by causing uterine relaxation. In my opinion, routine use of oxytocics has greatly reduced the necessity for packing. I agree with what Dr. Cosgrove has said.

DR. MUSSEY. (Closing.)—I am aware of the vast experience of Drs. Cosgrove, Baer, and Bill, and appreciate their constructive criticism. I agree with Dr. Bill, as we have mentioned in the paper, that prophylaxis is of primary importance in this condition and that management of the third stage should be conducted with a minimum of manipulation of the uterus.

However, my colleagues and I feel that the use of the intrauterine pack has a place in the management of postpartum hemorrhage. This position is upheld by a majority of writers on this subject and has been approved by Dr. Campbell, Dr. Montgomery, and others today. Our distinguished friend from Holland states that in his country little or no analgesia and anesthesia are employed in labor. I agree with him that the use of these agents seems

to increase the incidence of postpartum hemorrhage. If expectant mothers were fully aware of the risk of their employment in labor there would be less demand for their use.

I may repeat that we have given pituitrin intramuscularly for many years as the baby is being delivered, and in the last ten years we have usually given an aseptic ergot preparation intravenously after the third stage is completed.

We have employed the intrauterine iodoform gauze pack in some cases in which bleeding appeared to be under control, but in which the uterus remained atonic. Many of our staff use the pack more often than is urgently necessary, but they have learned that the early application in the uterus of a washed iodoform gauze pack in cases of uncontrolled or poorly controlled postpartum bleeding, and in the presence of an atonic uterus is much safer than to delay and permit the patient to slip into a condition of shock. Also, we believe that blood transfusions should be used to prevent shock as well as to treat it.

I failed to mention that the pack usually is removed on the morning following its insertion, so that usually it remains in place from, perhaps, four to thirty hours. An iodoform gauze pack which is removed from the uterus, as described, does not have a foul odor. When the occasion arises we employ the intrauterine iodoform gauze pack with caution but without dread.

MATERNAL CONGENITAL HEART DISEASE AS AN OBSTETRIC PROBLEM*

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HEART disease is displacing infection, hemorrhage and toxemia as leading causes of maternal mortality.[1] The death rate from heart disease in pregnancy is declining too but at a slower rate. Since rheumatic heart disease is by far the most common cardiac disease in pregnancy, it has received the most attention.

Congenital heart disease is uncommon in pregnancy but it is by no means as rare as the older literature suggests. In 1938, Jensen[2] reviewed the literature and recorded 115 cases. Almost all were in the form of single case reports. However, since that time, Hamilton and Thomson[3] described twenty-eight more. Other authors[1, 4] have reported a score or more. These numbers forecast an increasing frequency of this complication. The increase is likely more apparent than real because of better skill in recognizing these lesions.

For the present at least, management of rheumatic heart disease in pregnancy is more or less satisfactorily standardized. Now other forms of heart disease require similar study. Do pregnant women with congenital heart disease present a problem similar to those with rheumatic disease? If not, what are the differences? It is the purpose of this paper to show that differences do exist not only between the various types of heart disease but also within the group of congenital lesions.

Observations

During the past ten years, twenty-five women have been admitted to the University Hospitals of the University of Minnesota Medical School because of pregnancy complicated by congenital heart disease. These mothers were delivered of twenty-nine babies in this clinic. Several had been delivered elsewhere earlier so that a total of forty-five deliveries was recorded for the group.

Age and Parity.—As might be expected with congenital heart disease, the patients were comparatively young (Table I).

TABLE I. AGE AND PARITY

PARITY	AGE IN YEARS				
	BELOW 20	20-24	25-29	30-34	TOTAL
Primiparas	1	8	5	1	15
Multiparas	2	5	5	2	14
Total	3	13	10	3	29

Complications of Pregnancy.—As a group, these were not unusual (Table II). The ominous complications of anemia and infection were common.

Toxemia of pregnancy was a frequent and serious complication. There were eight patients with hypertension but only five had other confirmatory evi-

*Presented by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seigniory Club, Montebello, Quebec, June 17 to 19, 1947.

TABLE II. COMPLICATIONS OF PREGNANCY

Anemia (hemoglobin below 10 Gm.)	6
Toxemia	5
Cleft palate	2
Pyelitis	2
Respiratory infection	1
Schizophrenia	1
Multiple pregnancy	1
Diabetes	1
Total	19

dence of toxemia. Mild pre-eclampsia, present in three cases, was not a serious problem. Severe pre-eclampsia was associated with congestive failure in its two appearances and was indirectly associated with the only maternal death.

Abortion.—None was observed. There were no therapeutic abortions.

Labor.—Spontaneous premature labor and delivery were common. Exclusive of two cesarean sections done before term, the incidence of premature labor was 22 per cent.

Labor was induced at term twice—once because of an excessive sized fetus in a woman with previous history of dystocia from large babies. The second induction was for severe pre-eclampsia.

Prolonged or difficult labors were not a problem. In fact, the descriptive term, "easy labor" was found on thirteen records. Table III shows the duration of the first and second stages. Three of the patients had precipitate labors and precipitate delivery in bed before they were fully aware of the reality of their labor.

TABLE III. DURATION OF LABOR

HOURS FIRST STAGE		PRIMIPARAS	MULTIPARAS	TOTAL
	3	1	4	5
3	6	5	4	9
6	9	4	2	6
9	15	2	1	3
15	21	3	0	3
21	24	1	0	1
Total		16	11	27*
MINUTES SECOND STAGE				
	10	3	4	7
10	20	2	4	6
20	30	6	2	8
30	40	3	1	4
40	60	2	0	2
Total		16	11	27*

*Two patients were delivered by cesarean section.

It has been departmental policy to terminate labor by low forceps delivery to reduce the strain of the second stage of labor for all patients with heart disease. Table IV shows that this has been done only occasionally. This discrepancy is best explained by the short duration of the second stage of labor (Table III). There were two cesarean sections, one for acute fulminating pre-eclampsia, and the other to terminate the pregnancy of a patient with congenital heart block who was most difficult to manage medically.

Excessive bleeding post partum was not observed. Seventeen had an estimated blood loss of 200 c.c. or less. None was over 600 c.c.

TABLE IV. DELIVERY AND ANESTHESIA

DELIVERY	TOTAL DELIVERIES	TYPE OF ANESTHESIA			
		NONE	LOCAL	LOCAL + GAS	OTHERS
Spontaneous	19	5	2	9	3
Low forceps	8	0	2	5	1
Cesarean section	2	0	2	0	0
Total	29	5	6	14	4

Anesthesia (Table IV) was usually local with some gas analgesia with uterine contractions.

Maternal Mortality.—There was one maternal death in the series. A case summary appears later in this paper. Another died six months post partum of subacute bacterial endocarditis. This had developed early in pregnancy as a complication of a patent ductus arteriosus.

The Infant.—There were many premature infants: eight in twenty-nine deliveries, or an incidence of 27.5 per cent. Exclusive of the two delivered by cesarean section, the premature labor began spontaneously, frequently while the mother was hospitalized for care during the last trimester. No significant exciting cause could be determined.

Table V shows the distribution of infants according to weight and mortality. Those who did not survive were a set of stillborn macerated premature twins and one full-term infant. The unique circumstances of the only neonatal death warrant a short case summary.

TABLE V. INFANT WEIGHT AND MORTALITY

	1,500* TO 1,999 GM.	2,000 TO 2,499 GM.	2,500 TO 2,999 GM.	3,000 TO 3,499 GM.	3,500 TO 3,999 GM.	4,000 GM. AND OVER	TOTAL
Total live births	2	6	2	10	4	4	28
Neonatal deaths	0	0	0	0	0	1†	1
Survival	2	6	2	10	4	3	27

*There was one set of stillborn twins weighing 1490 and 1545 grams respectively.
†See text for details.

The mother was a secundipara, 26 years of age. She had known of her congenital heart disease for fifteen years. Her lesion was a ventricular septal defect, Class 2. There had been no change in her cardiac condition during pregnancy. She was referred to the University Hospitals, not because of her cardiac condition, but because she had had a very difficult labor with her first pregnancy. After two weeks of observation it was felt that the baby was becoming excessive in size so labor was induced. Following a one and one-half hour labor, she was delivered spontaneously of a 4,100 Gm. infant, who breathed immediately. The baby soon became cyanotic and died on the following day. Postmortem examination revealed a large ventricular septal defect! The mother has since had a normal infant, and she is living and well five years after her last pregnancy. A somewhat similar case has been reported by Tucker and Kinney.[5]

The remainder of our observations deal primarily with the effect of pregnancy on the congenital heart disease.

Etiology.—The relationship of such factors as heredity, maternal rubella in early pregnancy, and maternal dietary deficiency to the production of congenital heart lesions places the problem of etiology in the sphere of the obstetrician. It is not the purpose of this paper to discuss etiology, but attention is called to two facts: There was the mother with a ventricular septal defect who produced an infant with the same lesion, and secondly, two of the twenty-five women (8 per cent) had a cleft palate and hare lip associated with a patent ductus arteriosus.

Diagnosis.—The diagnosis of congenital heart disease most certainly falls outside the sphere of the obstetrician, and inevitably rests upon a competent cardiologist. This study is no exception. The final diagnosis (Table VI) has been based upon the opinions of the cardiologists in the Department of Medicine, and often their final diagnosis was not made until several weeks post partum. We are indebted to these consultants not only for diagnosis, but for invaluable assistance in the management of these patients.

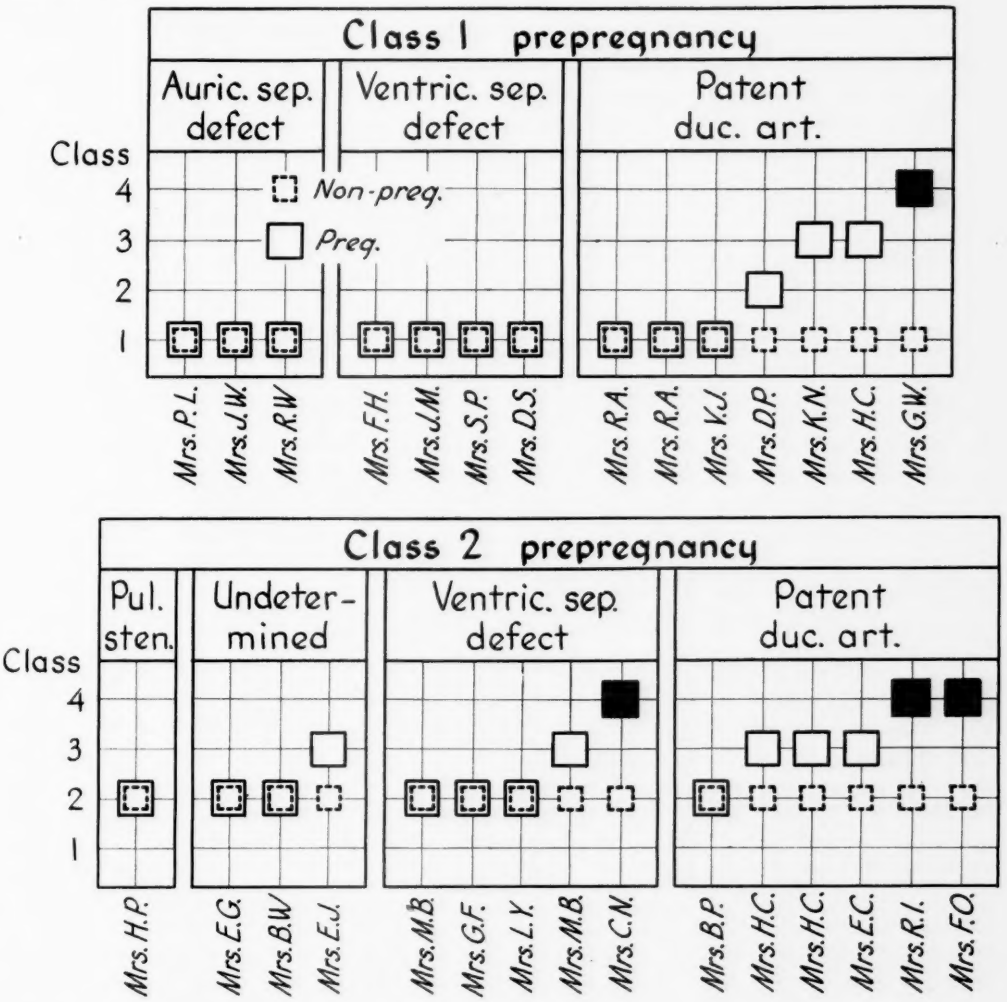

Fig. 1.—Changes in functional capacity in congenital heart disease in pregnancy. Each patient's class (New York Heart Association) before pregnancy and the maximum change produced during pregnancy is listed according to the type of lesion.

Only two points concerning diagnosis seem pertinent to this paper. The first concerns diagnostic accuracy. No patient was included in this study if there was doubt as to the congenital nature of her lesion. However, if comparisons are to be made between the various types of congenital lesions, then detailed diagnosis must be accurate. Table VII shows the relative merits of the common diagnostic criteria and their bearing on the final working diagnosis.

The second point of interest concerns the relationship of the obstetrician to the first diagnosis. Nothing more than a history was necessary to establish

TABLE VI. TYPES OF LESIONS

Patent ductus arteriosus	13
Intraventricular septal defect	8
Auricular septal defect	4
Pulmonary stenosis	1
Undetermined	3
Total	29

TABLE VII. EVALUATION OF DIAGNOSTIC FINDINGS

MURMUR		ELECTROCARDIOGRAM		X-RAY	
Characteristic	14	Abnormal	8	Characteristic	13
Suggestive	7	Normal	17	Suggestive	9
Questionable	4			Questionable	3

Final Diagnosis

Reasonably certain	14
Probable	7
Possible	4

a tentative diagnosis of organic heart disease in twenty-three of the twenty-five patients. Only two had the diagnosis made for the first time during pregnancy. In five, the diagnosis was as recent as five years, but the remainder had known of their cardiac condition for many years. Present-day attention to cardiac lesions in infancy and childhood will probably record most of these abnormalities at an early age and long before pregnancy occurs.

Functional Capacity or Cardiac Class.—All patients were catalogued according to the functional classification of the New York Heart Association (Class 1, 2, 3, and 4). Each patient was classified according to her prepregnant state for the purpose of establishing a base line. Then she was reclassified during the first part of pregnancy, the last trimester, labor and delivery, and finally after pregnancy.

Patients were separated according to the type of lesion and the prepregnancy class (Fig. 1). None was in Class 3 or 4 before pregnancy. Twelve of the twenty-nine pregnancies were associated with change in class. The greatest disturbance of class was associated with patent ductus arteriosus where nine of twelve patients exhibited change, and all but one of the Class 2 patients were worse. Only three other changes were noted: two associated with ventricular septal defect, and the other with an undetermined congenital lesion. (One cardiologist thought the latter definitely a ventricular septal defect.)

Even more information can be had by a chronological analysis of those who changed. Fig. 2 shows the amount of change in relation to the duration of pregnancy. Every patient who maintained her prepregnant class through the first part of pregnancy changed no more than one class later in pregnancy. As there were no Class 3 prepregnant patients, this means that no patient of this type failed. On the other hand, every patient who changed in early pregnancy changed one or more classes later. The more serious changes were associated with patent ductus arteriosus.

Fig. 2 also shows the permanent change in class associated with pregnancy. Four mothers never returned to their prepregnancy levels. All had patent ductus arteriosus. Two mothers in Class 1 became Class 2 post partum, and two in Class 2 become Class 4 and ultimately died—one during cesarean section, and the other six months post partum.

Pulse and Respirations.—In 1942, Mendelson and Pardee[6] claimed prognostic significance to the rate of pulse and respirations of mothers with rheumatic heart disease during the first stage of labor. They believe that the criti-

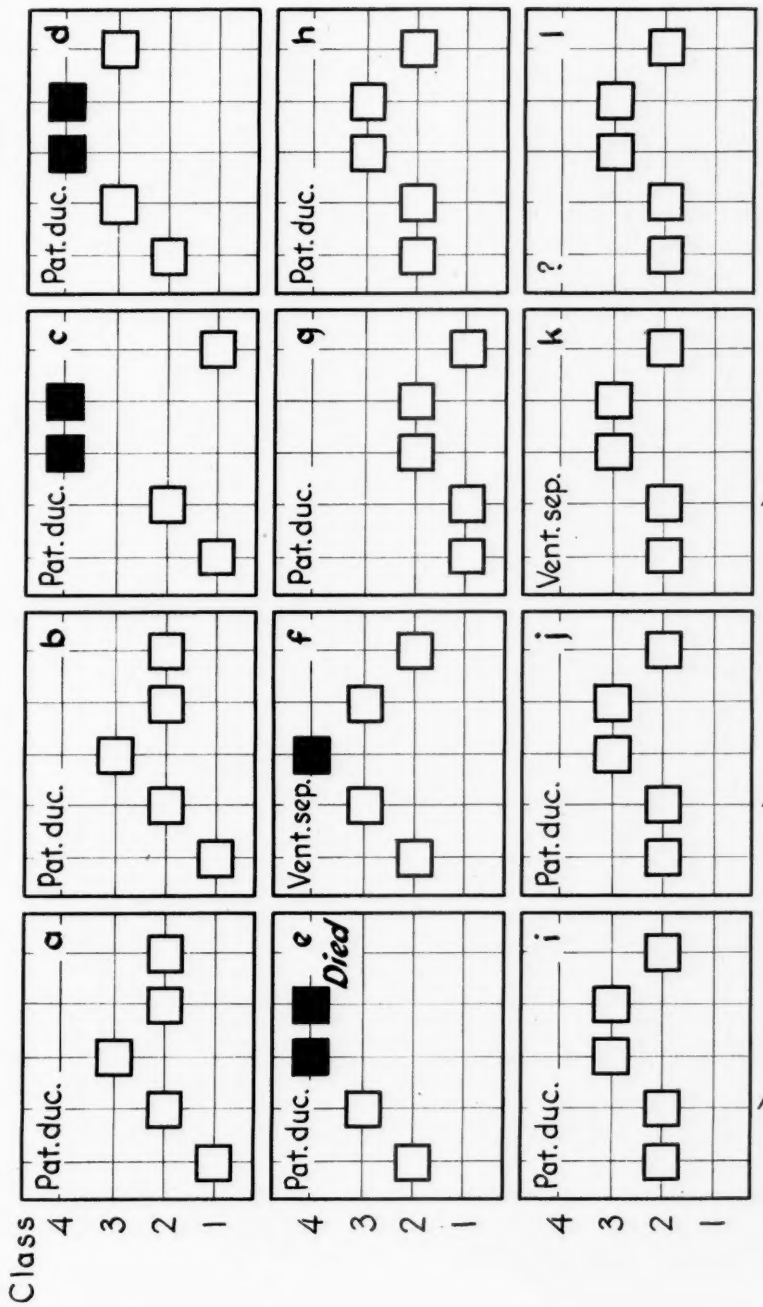

Fig. 2.—Changes in functional capacity in congenital heart disease in pregnancy. This shows the change in class according to duration of pregnancy. Note the unfavorable course of patients a-f whose class changed in early pregnancy.

cal levels are 110 and 24 for pulse and respirations, respectively. When rates exceeded these levels, the patient was in imminent danger of heart failure. An attempt was made to review the validity of this rule for congenital disease. Each patient was studied before labor, during labor, delivery, and the puerperium. It must be pointed out that we were unable to obtain readings routinely every fifteen minutes as is suggested. However, the data were quite complete for Class 3 and 4 lesions. Two of the Class 4 patients were always below the critical levels; however, one had a heart block, and the other was digitalized. The other two Class 4 patients had positive findings. There were three Class 3 patients with pulse and respirations above the critical ranges. None failed, but one was dangerously near it. Also, two Class 1 and two Class 2 patients exceeded critical levels without signs of cardiac embarrassment.

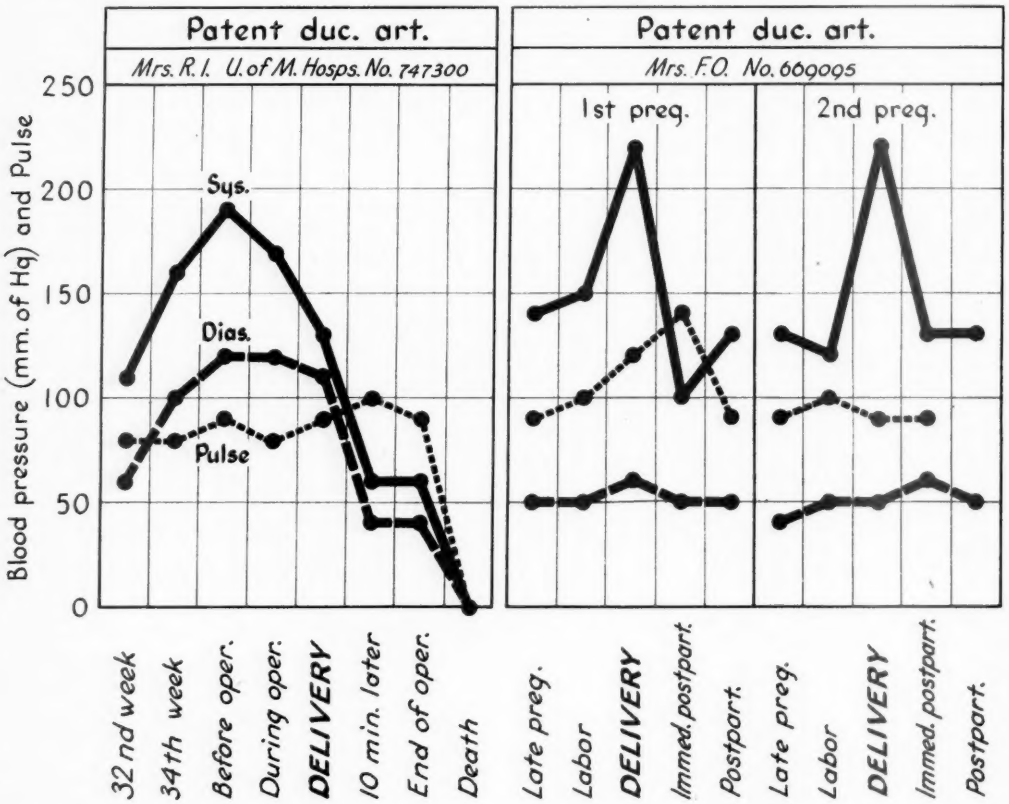

Fig. 3.—Changes in blood pressure during labor and delivery. The shocklike picture which may be associated with delivery is demonstrated. A detailed report of Mrs. R. I. is found in the text. Mrs. F. O. showed similar reactions in two successive pregnancies.

Blood Pressure.—Eight of the patients presented bizarre changes in blood pressure during delivery. In general, the reaction consisted of hypertension followed by a sudden drop in blood pressure to low levels immediately after delivery of the baby.

The hypertension was sometimes present before labor because of toxemia. In others, the hypertension developed spontaneously during labor. In a very few minutes after the baby was delivered—sometimes before and sometimes after the placenta was delivered—the blood pressure dropped dramatically. Three patients lost consciousness. All but one recovered within a few minutes, or at most a few hours. Table VIII lists the details. The labile blood pressure

was most common with patent ductus arteriosus, but it was seen with septal defects as well. With one exception, the break occurred in patients of Class 3 or 4. Figs. 3 and 4 illustrate individual patients. From Table VIII it is interesting to note that the shock was unrelated to hemorrhage or to pituitrin. One patient exhibited strikingly similar changes in two successive pregnancies (Fig. 3).

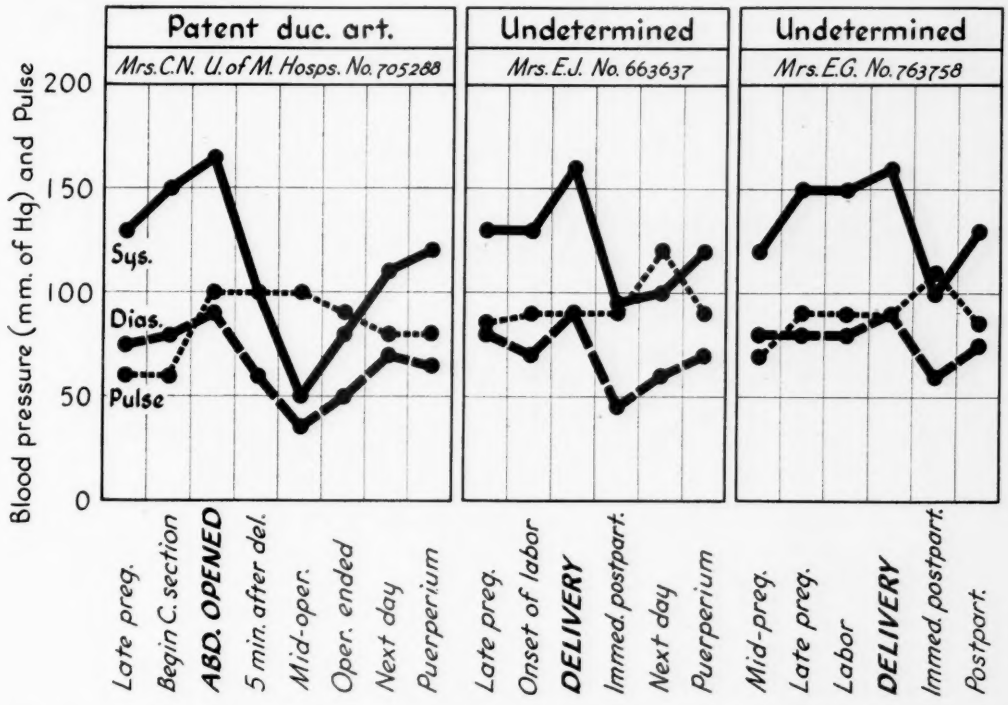

Fig. 4.—Changes in blood pressure during labor and delivery. The hypertension-delivery-shock syndrome similar to Fig. 3.

The following case history describes this picture adequately: A primigravida, aged 26 years, knew she had heart disease as a child. Her only symptom had been dyspnea on moderate exertion. She was first seen at the twenty-fourth week of pregnancy, and a diagnosis of patent ductus arteriosus was made. After complete work-up, she was digitalized, and her activities were markedly restricted. At the thirty-second week, she was progressing nicely without symptoms. Arrangements were made for admission to the hospital for the remainder of the pregnancy, but the patient refused. Two weeks later she suddenly developed edema of feet, hands, and eyelids, dyspnea at rest, orthopnea, and slight cyanosis. Blood pressure, previously 115/60-80, was now 165/100. There was marked albuminuria. She was admitted to the hospital and actively treated for pre-eclampsia. In spite of all therapy, the blood pressure rose rapidly to 200/120, and eclampsia was imminent. The cervix was long, hard, and closed so the only feasible method of delivery was by cesarean section. The operation was done under local anesthesia. Fig. 3 shows the behavior of blood pressure and pulse during operation. The patient remained in shock for about half an hour with a relatively slow pulse and died. Postmortem examination revealed a patent ductus arteriosus of such magnitude that there was no duct—merely a hole about 1 cm. in diameter between the left branch of the pulmonary artery and the aorta. The right ventricle showed massive hypertrophy being 22 mm. thick, as compared to 14 for the left ven-

TABLE VIII. BLOOD PRESSURE DURING LABOR AND DELIVERY

PATIENT	LESION	HIGHEST CLASS	BLOOD PRESSURE					BLOOD LOSS IN C.C.	OXYTOCIC	LOSS OF CONSCIOUSNESS	REMARKS
			LATE PREGNANCY	LABOR	DELIVERY	IMMEDIATELY POST PARTUM	PUERPERIUM				
N. C.	Patent Ductus	3	140/50	150/50	220/60	100/50	130/50	100	Pituitrin	0	
N. C.	Patent Ductus	3	130/40	120/50	220/50	130/60	130/50	50	Ergot	0	Repeat performance. See above
E. J.	Patent Ductus	3	130/80	130/70	160/90	95/50	170/70	300	Ergot	Yes	Marked anxiety
F. O.	Patent Ductus	4	120/60	110/60	120/60	90/60	130/60	400	Ergot	0	
R. I.	Patent Ductus	4	160/100	190/120*	130/110†	60/40	----	400	Ergot	Yes	Toxemia. Died. Cesarean section
C. N.	Vent. Septal	4	130/75	150/80*	165/90†	50/35	120/70	300	Ergot	Yes	Cesarean section
E. G.	Undetermined	2	150/80	150/80	160/90	100/60	130/75	150	Ergot	0	Mild toxemia
Hypertension Without Sudden Postpartum Change											
D. S.	Vent. Septal	1	150/105	150/105	160/100	150/105	160/110	200	Ergot	0	Toxemia
D. P.	Patent Ductus	2	115/55	130/60	180/80	170/80	115/60	300	Ergot	0	
G. W.	Patent Ductus	4	180/84	200/80	225/85	190/80	135/65	150	Ergot	0	Toxemia

*Beginning operation.
†After delivery.

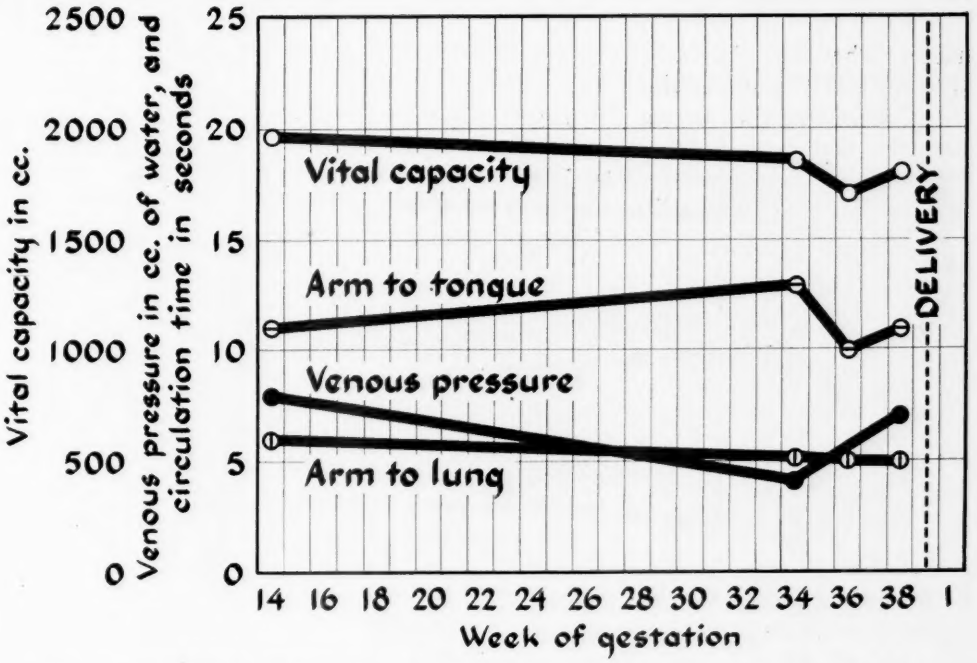

Fig. 5.—Circulation studies in congenital heart disease. This patient, Mrs. E. G., a Class 2 cardiac, went through pregnancy without event. The vital capacity, venous pressure and circulation times were normal throughout.

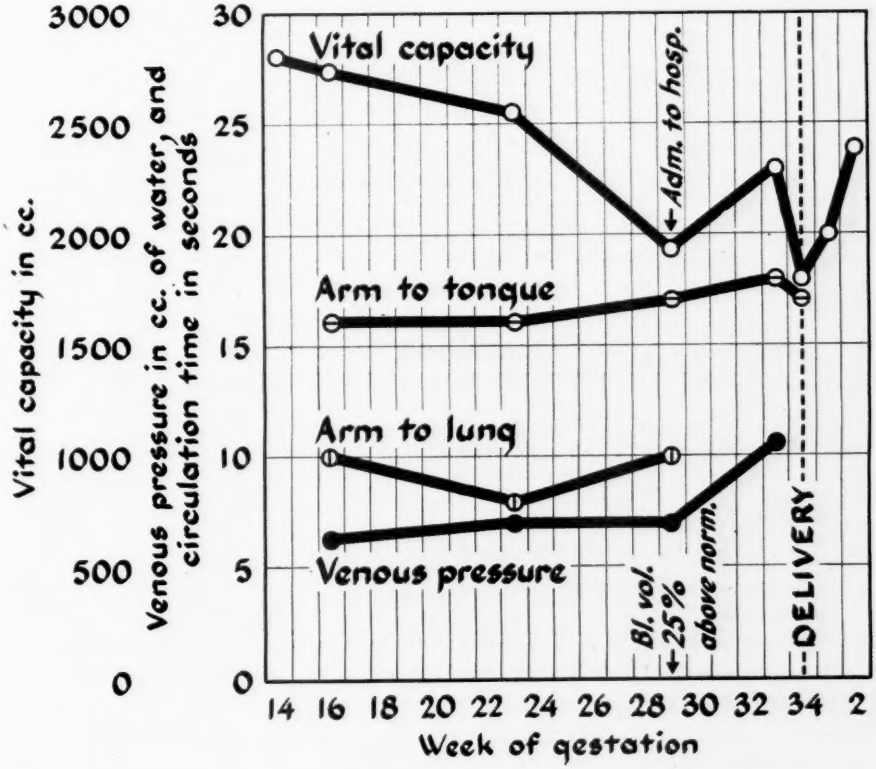

Fig. 6.—Circulation studies in congenital heart disease. Mrs. V. J. showed a decreasing vital capacity which suggested a diminishing cardiac reserve. Hospitalization and bed rest produced improvement as manifested by increasing vital capacity.

tricle. The liver showed the characteristic necrosis of eclampsia. Other findings were not remarkable.

Vital Capacity, Venous Pressure, and Circulation Times.—These tests were made on many patients. They are now done routinely on all patients except those with very minor lesions. While these tests may have some diagnostic value, they are being used primarily as aids in predicting impending failure.

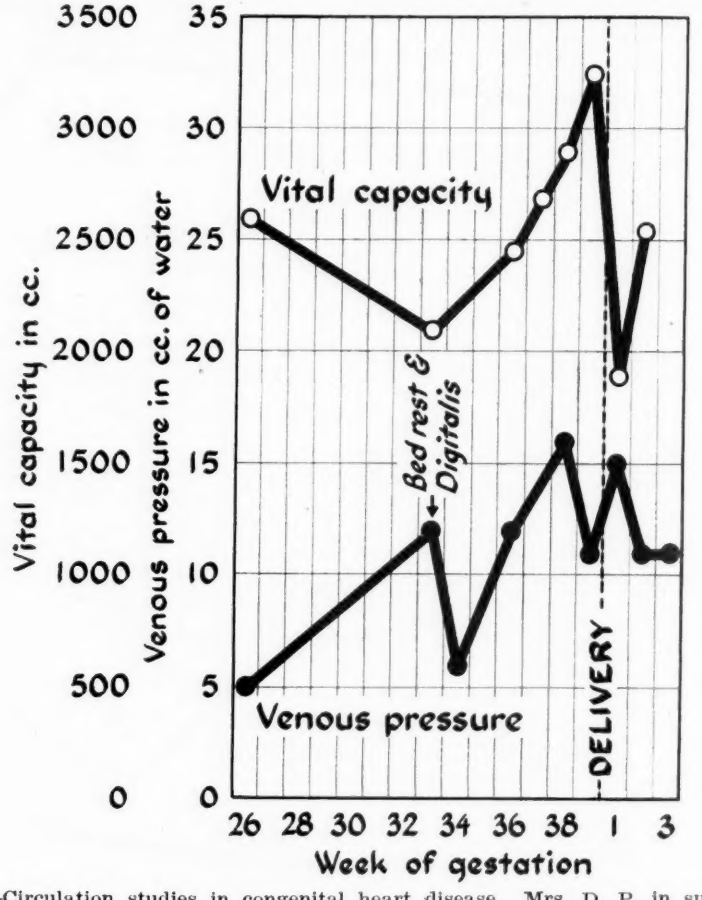

Fig. 7.—Circulation studies in congenital heart disease. Mrs. D. P. in spite of limited activity, the vital capacity decreased and venous pressure increased. There was no clinical evidence of heart failure. However, after bed rest and digitalis she improved.

Vital capacity is easy to determine. Results have been more readily obtained and more accurate since we utilized the spirometer of the ordinary basal metabolism machine. With this method it is possible to have an accurate graphic measurement for inspection. Furthermore, some notion of cooperation on the part of the patient could be seen. For example, one patient showed a sudden drop of 400 c.c., but the graph indicated it was a poor attempt. Investigation showed the patient to be dissatisfied because of prolonged hospitalization, and the record was discarded. Maximum value of this and other similar tests is obtained when observations are begun early in pregnancy and repeated at monthly intervals. Later, they may be done weekly as the load of pregnancy increases.

In a similar manner, base line values for venous pressure and circulation times were established. The tests were repeated with increasing frequency as pregnancy advanced.

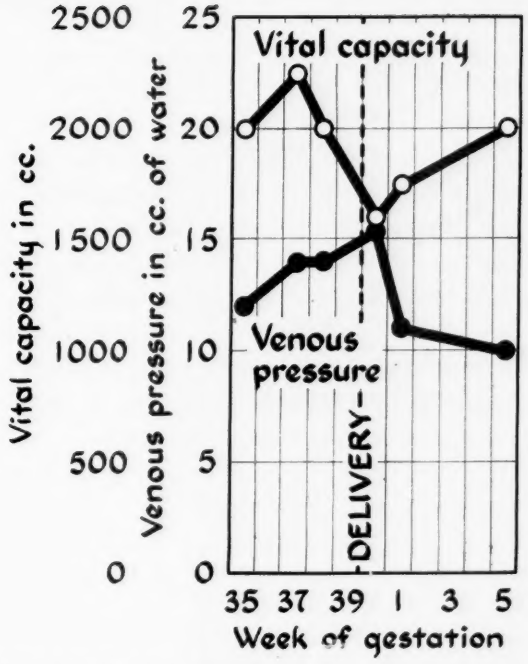

Fig. 8.—Circulation studies in congenital heart disease. Mrs. L. Y. The decreasing vital capacity and increasing venous pressure suggests that peak load was at delivery in this patient. She did not decompensate.

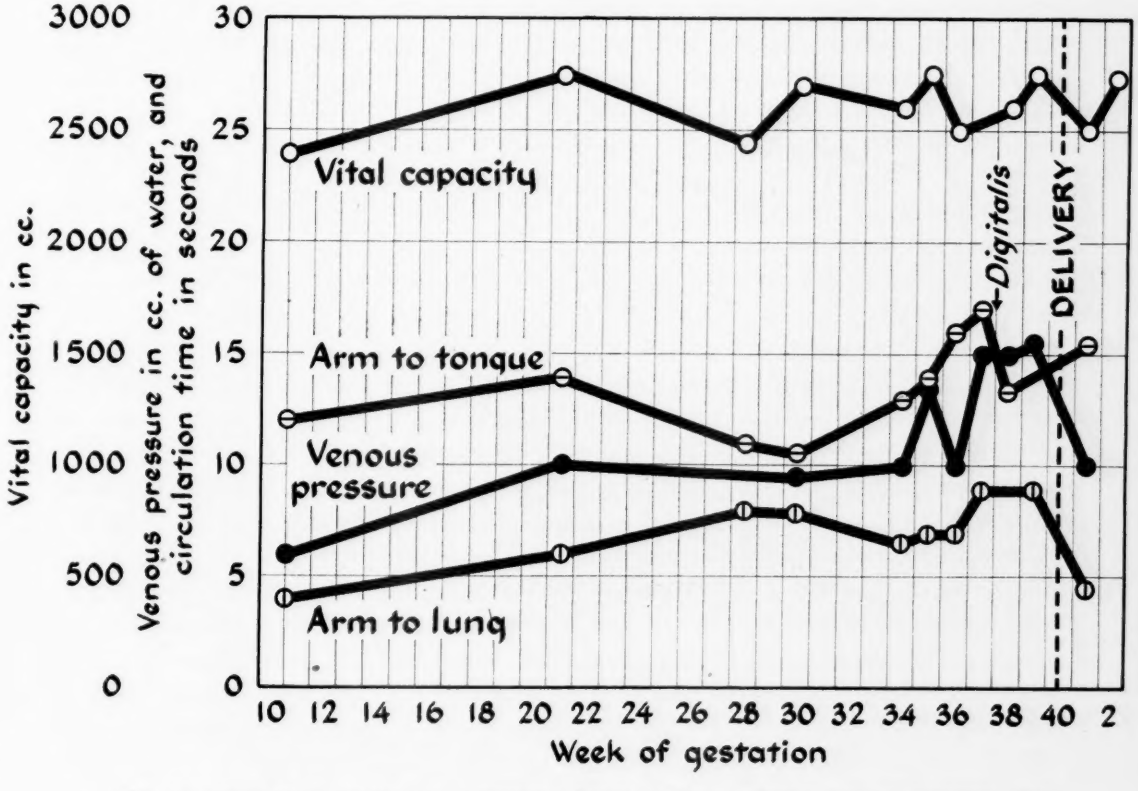

Fig. 9.—Circulation studies in congenital heart disease. Rising venous pressure and arm to tongue circulation time suggested a diminishing cardiac reserve. Some improvement followed digitalization. Vital capacity did not change.

Space does not permit presentation of the detailed records of all patients. Figs. 5, 6, 7, 8, and 9 show results obtained from such measurements.

Discussion

The management of all types of heart disease in pregnancy is intimately related to the increased burdens placed upon the heart. These are but two—the inevitable and the incidental loads. The *inevitable* load comes from the augmented blood volume which increases the minute volume output of the heart, the increase in oxygen consumption as manifested by elevated basal metabolism, the strain of delivery, whether vaginal or by cesarean section, and the puerperium. The *incidental* load may come from a variety of sources such as infection, obesity, anemia, physical and mental strain, etc.

Does the pregnant woman with congenital heart disease have these same loads? Does she have additional ones? And finally, does she react to them differently than do women with rheumatic disease?

Many of the usual incidental loads were common to these patients. Some mothers were made worse by anemia or by excessive weight gain or by infection. The importance of these common complications is so well known that further comment is unnecessary.

Special mention must be made of toxemia of pregnancy. Hamilton and Thomson[3] and Henderson[7] have emphasized the gravity of toxemia in mothers with heart disease. It occurs at the time of peak physiologic load and thus strikes the heart at the most vulnerable time. This study shows the gravity of toxemia in patients with congenital lesions. Five patients had patent ductus arteriosus, and both developed congestive failure after the rapid onset of the toxemia. This suggests that a rapidly developing toxemia in a person with a large congenital defect throws a burden not only on the left side of the heart, but also on the right because of the shunt through this defect. Prompt attention to the mildest toxemia is imperative and, should conservative measures fail, the patient becomes a candidate for termination of pregnancy before serious cardiac strain has had an opportunity to develop. Toxemia may be an even greater hazard in congenital heart disease than it is in rheumatic heart disease.

Most of the incidental loads can and should be recognized by careful prenatal observation, and controlled partially or completely by careful management. Need for hospital care at the slightest abnormal sign must be emphasized. It is not unusual for these patients with the serious forms of congenital heart disease to need hospitalization during the entire last trimester. In this way it is possible to reduce the incidental load at the time of peak inevitable load.

There is no symptom, no sign, no laboratory test which can give definite accurate information about the cardiac reserve of all patients. On the other hand, there are many subjective and objective findings which frequently give valuable assistance. It is important to exhaust these possibilities to the point of diminishing returns in all pregnancies complicated by heart disease to achieve a minimal maternal mortality.

It is not necessary to review all of these studies in detail, but the significance of some are worthy of emphasis.

We have adhered to the New York Heart Association method of cardiac classification and agree with Mendelson[8] concerning the advantages of this method.

First, it is important to know the class before pregnancy so that it can be correlated with the type of lesion and changes of class during pregnancy. With the exception of those with patent ductus arteriosus, no Class 1 patient worsened during pregnancy. The importance of the prepregnancy class was shown in another manner. No patient failed during pregnancy or delivery if she maintained her prepregnancy class through the first six months of gestation; but every patient who deteriorated one class from her prepregnant level during early pregnancy (six months), also deteriorated one or more classes in late pregnancy. All who failed exhibited such a change in early pregnancy; and all but one had patent ductus arteriosus. Finally, there was the return of the patients to nonpregnant levels. Four failed to return to prepregnant levels. Again all of these had patent ductus arteriosus.

Of the various objective tests for showing changes in cardiac reserve, the calculation of vital capacity has been the most helpful—especially in mothers with patent ductus arteriosus. If vital capacity is compared from patient to patient, it must be done by calculations based on surface area, which, incidentally, have never been done for the pregnant woman. To obviate this difficulty, we have been content to depend upon the change in vital capacity in a given patient. It has been established that there is an increase in vital capacity during normal pregnancy.[9] With the accuracy of the method described above, we believe, as do Hamilton and Thomson[3] that a progressive decrease of more than 10 per cent may be significant.

Another patient may have no significant change in vital capacity, but increasing venous pressure, or circulation times may presage impending failure. Fig. 9 shows such pattern. As soon as a threat of failure was obtained, the patient was digitalized, activity was completely restricted, and she improved and completed pregnancy satisfactorily. Nearly everyone is aware of the errors which may invalidate these determinations. But, in spite of these drawbacks, tests occasionally help to pick the patient who is headed for congestive failure before customary signs and symptoms are present.

One of the distinct hazards for women with congenital heart was the strange sudden changes of blood pressure which frequently accompanied disease delivery. It would seem that preliminary hypertension is an essential part of the syndrome. Toxemia was frequently the cause. On the other hand, several patients had an unexplained increase in blood pressure during labor without the presence of toxemia. Regardless of cause, it would seem reasonable to expect that sudden hypertension in the peripheral circulation would be felt in the pulmonary circulation if a large defect existed either between the pulmonary artery and the aorta or between the right and left ventricles. This preliminary hypertension, present in all but one of the group under discussion, reached a peak at about the time of delivery. Then a few minutes after the

uterus was emptied, the blood pressure dropped suddenly. All but one patient recovered, but several were in a critical condition. The nature of this mechanism is not clear, but the most likely explanation is that the sudden drop in peripheral blood pressure is accompanied by a reversal of blood flow through the congenital defect. With peripheral hypertension there would be at least temporarily an increased arteriovenous shunt, then with the shock of delivery, a reversal with the production of a venous-arterial shunt. The possibility of this mechanism was postulated by Abbot, quoted by Jensen,[2] who said he had never heard of an actual case reported. Hamilton and Thomson[3] reported three patients who died of shock following shocking operative procedures such as cesarean section and version and extraction. No detailed information as to blood pressure was given. Certainly shocking operative procedures can be a factor in this syndrome. However, similar changes happened twice in the same patient (Fig. 3), and she was delivered spontaneously with ease. The size of the defect must be important, and this was confirmed in one patient by autopsy. She had an enormous patent ductus arteriosus. Of significance, too, is the functional class. With one exception, every patient, who had the hypertension-shock syndrome, was in Class 3 or 4 at the time of delivery. There was no correlation with pulse and respiratory rate.

Just why three women with hypertension did not develop shock is not known. Perhaps it was because the lesion was small and the cardiac reserve good.

Little is known concerning therapy. Hamilton and Thomson[3] have suggested binding of extremities. This is worthy of trial, but we have not done so. Therapy in this series was merely supportive with oxygen, digitalis, and similar measures. Of greater importance is to watch for hypertension during labor and to be unusually cautious with operative or other shocking methods of delivery in such patients.

Finally, the data should be considered according to the anatomic lesion.

Patent Ductus Arteriosus.—This was the most serious lesion in this study. All but one of the failures and the only death were associated with this defect. Many of these patients grew worse during pregnancy, and four remained permanently worse. The syndrome of hypertension and shock at delivery was common. These observations are at variance with those of Hamilton and Thomson,[3] who found a patent ductus arteriosus to be less serious than a ventricular septal defect.

Ventricular Septal Defect.—This was also a serious complication, but not so serious as patent ductus arteriosus. One of this group failed and nearly died. Those with the milder forms of the disease withstood pregnancy well.

Auricular Septal Defect.—This produced no serious problems in the three patients of this group.

Pulmonary Stenosis.—Only one patient was so diagnosed, and she tolerated pregnancy without serious difficulty.

As a group, those with patent ductus arteriosus and ventricular septal defects were problems, but it is likely that the size of the lesion and the cardiac reserve are more important than the anatomic lesion.

Finally, we must give some thought to the future, particularly as it concerns the surgical treatment of congenital defects. Girls who now are having

a patent ductus arteriosus ligated should present no problem at the time of pregnancy; but we are apprehensive about those who are now having surgery for tetralogy of Fallot and who will wish to have babies ten years from now. Until more information is available, it would seem wise to consider these people as serious cardiac risks, and pregnancy should be undertaken only with extreme caution under constant observation.

Summary and Conclusions

Twenty-nine pregnancies have been observed in twenty-five patients having congenital heart disease. The pregnancy in general was not adversely affected. Toxemia was rather common and proved to be a very serious complication. The incidence of premature delivery was high at 27.5 per cent. Labor and delivery were never difficult, and half were described as being rapid and easy. All deliveries but two were by the vaginal route under local anesthesia.

There was one maternal death, a patient with patent ductus arteriosus and severe pre-eclampsia. There was one neonatal death—an infant with a ventricular septal defect whose mother had the same type of lesion.

The effect of pregnancy on congenital heart disease was frequently different from that on rheumatic heart disease. There was considerable variation in effect within the group according to the type of defect. Those with patent ductus arteriosus were most seriously affected. Moderate change was noted in those with ventricular septal defects, while those with auricular septal defects and the one with pulmonary stenosis were little changed.

The New York Heart Association's classification was used, and it proved to be valuable. All patients who changed from their prepregnant class to a higher class in early pregnancy went on to an even higher class later in pregnancy. All of those who failed were in this group.

The use of vital capacity, venous pressure, and circulation times were sometimes of value in predicting the development of congestive failure.

Strange changes in blood pressure at the time of delivery were found in 25 per cent of the group. The syndrome usually was manifested by hypertension reaching its peak at delivery and then sudden shock after delivery. One patient died following this reaction. The suggested explanation is a sudden shunt of blood from the right side of the circulation to the left because of drop in peripheral pressure.

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Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—The paper of Dr. Lund has reported a large series of these relatively rare cases. Very few of us have had personal experience with any large series from which to draw conclusions.

In our clinic we have had seven patients who have delivered fifteen babies. One of these patients died, the others survived. I will briefly indicate the results that we obtained in these cases. The first was a 37-year-old primipara. The disease had been recognized since she was 3 years of age. The type of lesion was not diagnosed and this woman died. Attacks of dyspnea were frequent during the pregnancy. She had a blood pressure of 146/96 and a 3-plus albumin. We hospitalized her Dec. 14, 1945, and planned to do a section four days later, but she was so much improved at that time that we waited, and this was probably a fatal mistake. The membranes ruptured suddenly on December 23 and she delivered in two and one-half hours. The baby weighed 3 pounds and survived. The mother was given oxygen during delivery and afterward, and survived the delivery in remarkably good condition. The toxemia improved, there was less albumin, blood pressure was lower, but her heart condition did not improve, and she suddenly died on Dec. 31, 1945. One might question whether she should be classified as an obstetric or a cardiac disaster. Women with congenital heart disease seldom live more than 38 years without the strain of pregnancy.

The second patient had been a blue baby. She was a primipara. She had dyspnea on exertion more or less all of her life. She had a vital capacity of 93. She had an arcuate type of uterus. She was admitted in the twenty-fourth week of her pregnancy, was kept in the hospital, and had bed rest from January 7 until March 3 and was delivered by cesarean section under local anesthesia. She and the baby both survived.

Another patient, 22 years old, had a toxemia shown by a blood pressure of 174/104 the night of the labor. There was no evidence of cardiac decompensation throughout the pregnancy. She had had scarlet fever, chickenpox, measles, whooping cough, but no endocarditis. She entered the hospital in labor with 8 cm. dilatation, and delivered spontaneously three hours later. Both she and the baby survived. She had had a previous delivery in June, 1942, the child weighing 6 pounds 4 ounces.

I will not read the other histories of patients on whom I have some notes, but will use this minute to emphasize some of the points made in the paper. As the essayist has indicated, these patients usually die of cardiac disease at a young age. Premature labor has been frequent in our experience. Induction of labor we think is questionable, because, if the induction does not succeed, a long labor under these circumstances is very bad. We believe that one should wait for spontaneous labor, particularly because if infection should be introduced by vaginal manipulation, it would not be well combatted.

Local anesthesia should be used, and one should prepare for a premature infant. The internists see few of these patients, and relatively little help can be obtained from them. This is because they have not watched these patients go through pregnancy and labor, therefore the management lies more with the obstetrician who because of previous experience knows more about how the heart will act in these cases than does the internist.

DR. BAYARD CARTER, Durham, N. C.—I would like to know how Dr. Lund classified his patients with congenital heart disease, also whether he considers patent ductus arteriosus a congenital anomaly of the heart or of the blood vessels. It would also be interesting to know the type of delivery and the form of anesthetic employed in managing these patients.

We have had during the years 1942 to 1946 the following patients with various forms of congenital heart disease:

1. Dextrocardia—two patients.

A. Negro, married, aged 29 years, para 5-0-5. No prenatal, delivery, or postpartum complications. She had two spontaneous uncomplicated deliveries in our care. She is now para 7-0-7.

B. White, married, aged 27 years, para 2-0-2. No complications in any of her three pregnancies under our care other than moderate hypertension in the third pregnancy. She is now para 5-0-5.

2. Patent ductus arteriosus—three patients.

A. White, single, aged 23 years, para 0-0-0. Elective cesarean section in first delivery (1946) for large child, small pelvis. The ductus was ligated (1947). She has imposed upon herself voluntary sterility, and we have not had the opportunity to follow her in another pregnancy.

B. White, married, aged 25 years, para 1-0-1. Uncomplicated prenatal course and spontaneous parturition (1942). Has not been seen since 1942.

C. White, single, aged 13 years, para 0-0-0. Ductus ligated in May, 1945. Uncomplicated prenatal course. Low forceps delivery at term, May, 1947. Normal course.

3. Congenital subaortic stenosis—one patient.

A. White, single, aged 19 years, para 1-1-0. Had performed elsewhere "therapeutic abortion." Seen by us in second pregnancy at eight and one-half months. Advised to go to term. Delivery elsewhere normal in all details.

4. Eisenmenger syndrome—one patient. (Dextroposed aorta overriding an intraventricular septal defect.)

A. White, married, aged 23 years, para 0-0-0. Admitted February, 1947, for early incomplete abortion. Induction of abortion denied by the patient. A dilatation and curettage had to be done for bleeding. Course normal. In this patient the question of tetrology of Fallot was debated.

5. Congenital heart block—one patient.

A. White, married, aged 33 years, para 0-0-0. Seen in seventh month of first pregnancy. No complications in prenatal course. Delivery spontaneous and course uneventful.

We agree with Dr. Lund that we should classify these patients as accurately as we attempt to classify patients with rheumatic heart disease. The prenatal course should be rigorously supervised. The conduct of labor should be free of the tendency to worry too much concerning the process of parturition and should emphasize the physiology of the congenital anomaly.

DR. LUND (Closing).—The patient that Dr. Falls presented emphasizes, by her unfortunate accident, the danger of toxemia in congenital heart disease. We have a feeling that a patient with any form of toxemia should be very carefully observed and, if necessary, be considered for interruption of pregnancy.

I agree with both discussants in the importance of the obstetrician knowing about heart disease. The obstetrician must know something about the way a patient who has heart disease behaves during pregnancy and labor.

I will have to pass the question asked by Dr. Carter as to whether patent ductus arteriosis is a disease of the vessels or of the heart. We have had no patients with dextrocardia.

Most of the patients were delivered under local anesthesia. A few had gas and local anesthesia, while some had nothing.

I would like to close with this thought: We are now seeing patients, young girls, who are having surgery done for the tetralogy of Fallot. They have a severe oxygen deficiency before surgery and are left with a concentration of 75 to 80 per cent after the surgery. These patients will be bad obstetric risks when they come to us within the next ten years. They must be carefully evaluated before undertaking pregnancy.

THE TREATMENT OF CERVIX CARCINOMA WITH RADIUM AND 800 KILOVOLT X-RAY*

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(From the Mercy Hospital Institute of Radiation Therapy and Loyola University School of Medicine)

DURING the ten-year period of 1933 through 1942 there were 422 patients suffering with carcinoma of the cervix admitted to the gynecologic service of the Mercy Hospital Institute of Radiation Therapy. It was at the beginning of this period that higher voltage x-ray therapy was first introduced at the Institute. The plan of radium therapy has remained the same since 1924. Therefore, a direct comparison of cases for the ten years of this study with the cases previously reported would show any advantage gained by the addition of higher voltage x-rays. It has been previously shown that an increase in the x-ray dose, due to improvement in technique, has given better permanent end results.[9]

In order to obtain an accurate opinion as to the effect of such therapy on cervical carcinoma, all recurrent cases and stump cancers were eliminated. They numbered two hundred fifty-six. It is quite agreed that previous irradiation alters the reaction of tumor cells to further therapy.[14] The treatment of recurrent and stump cancers will, therefore, be discussed in a subsequent presentation. This study will consider 166 cases that had no form of treatment before admission and are classed as primary.

The clinical grouping of these cases has been arranged according to the Schmitz classification[11] which is still in use in our clinic. The reason for our preference has been previously published and need not be repeated here.

Table II reveals 70 per cent of the cases to be in the later or unfavorable groups. It is hoped that this deplorable situation can be altered by the intensive lay educational programs now being carried on. It is our present opinion that we are seeing the patients earlier. No attempt has been made to determine the

TABLE I. CARCINOMA OF THE CERVIX, MERCY HOSPITAL INSTITUTE. 1933 TO 1942

Recurrent cases	256
Primary cases	166
Total	422

TABLE II. CLINICAL GROUPING OF CASES STUDIED*

Group I	11
Group II	37
Group III	70
Group IV	48
Total	166

*Schmitz Classification.

*Presented, by invitation, at the Seventieth Annual Meeting of the American Gynecological Society, the Seigniory Club, Montebello, Quebec, June 17 to 19, 1947.

age or delay period in these patients as such studies have been published and the age of greatest frequency of cervix carcinoma has been established.[11] The delay period is directly responsible for the extent of the disease in most instances. Four of the cancers in Group I were extremely early and were diagnosed by microscopic examination of the tissue removed at biopsy. It is our policy to remove tissue for microscopic examination from all suspicious areas before any treatment is undertaken.

TABLE III. MICROSCOPIC GRADING OF TUMORS (BRODER'S)

GRADE	NUMBER	PER CENT
I	4	2.4
II	51	30.7
III	52	31.4
IV	10	6.0
Adenocarcinoma	4	2.4
Not Graded	45	27.1
Total	166	100.0

The microscopic grading of the tumors was carried out according to Broder's[3] division into four grades. In 45 cases the pathologic reports did not carry a grading, and the tissue was not obtainable for review. A comparison of the remaining cases with the incidence of the three varieties of Martzloff,[6] which he gives as 15 per cent spinal cell, 66.8 per cent transitional, and 12.0 per cent spindle cell shows a slight difference. The middle groups or transitional cell type is about the same. We have frequently obtained different gradings from repeat biopsies of the same tumor and, therefore, have learned to expect variations. Adenocarcinoma was found in 5.4 per cent of Martzloff's series, while our incidence was 2.4 per cent. A previous study from our clinic showed a similar incidence. As to the influence of the cell type on survival rates or response to therapy, we are not convinced that it is as important as the clinical grouping. It is our policy to treat all cell types with x-ray and radium and to reserve the Wertheim operation for those cases that are refractory to irradiation or that recur. None of the cases in this series were treated by subsequent surgery because of recurrence.

Plan of Treatment

Both radium and x-ray are employed in the treatment of all cases in the first three clinical groups. In Group IV cases, x-ray is administered, as a palliative therapy and radium withheld entirely unless the tumor regression is marked and further therapy is thought to be advantageous. It is our policy to withhold radium in those patients showing bullous edema or definite invasion into the rectal or bladder mucosa. Routine cystoscopic and proctoscopic examinations are necessary to reveal such pathology and to diagnose other pathological conditions in the urinary tract which later may be accredited to the therapy. Pomeroy[8] found abnormal pyelographic findings in 16.2 per cent of 271 cases in which intravenous pyelographic examination was made before treatment of patients with carcinoma of the cervix uteri. If future examination reveals regression of

this extension with x-ray therapy then radium is used. It has been our impression that radium therapy contributed very little in these cases if they were refractory to x-ray.

By means of the measuring frame shown in Fig. 1, an exact outline of the pelvis of the patient to be treated is obtained. The depth of the tumor is now determined by use of calipers and this information plotted into the pelvic outline previously obtained.[12] As it is our desire to attain an x-ray dose of 4,000 r into the tumor and surrounding gland-bearing areas of the pelvis, the number of fields necessary are determined. Whenever possible we use but one anterior and one posterior field. The size of the field being 20 by 20 cm. or less, depending on the size of the pelvis. We desire to irradiate an area extending from the promontory of the sacrum to the symphysis and from one anterior superior spine to the other. Using 800 K.V. x-ray with 10 M.A. at 70 cm. F.S.D. and filtering with 1 mm. lead, 1.56 mm. tin, 2.62 mm. copper, 3 mm. aluminum + 2 mm. extension chamber, we obtain 44 r per minute on the skin. At 10 cm., measured in a presdwood phantom, we receive 56 per cent of this amount.

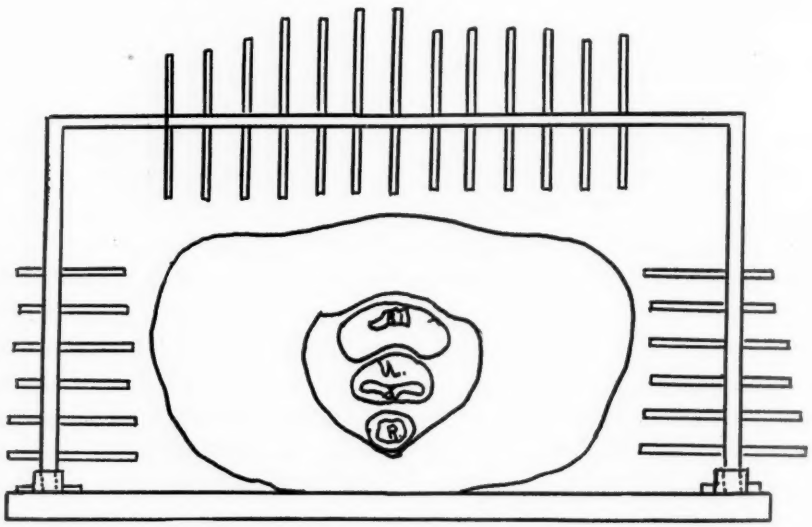

Fig. 1.—Caliper to obtain the topography of the pelvis and hips.

As our tolerance skin dose with x-rays of this intensity is in the neighborhood of 4,000 r, multiple fields are not necessary unless the patient measures over 20 cm. from anterior to posterior. If this be so, three or four fields are employed according to the need. Measurements made with a presdwood phantom using our 20 by 20 cm. field show that we lose in the neighborhood of 1 r at the outer margin of the field and with the 10 by 10 cm. field our loss is 0.4 r. This difference is so small that we prefer the massive homogeneous irradiation obtained through large ports. No special effort is made to screen out vital structures as this practice invites error due to misdirection of the radiation beam.

Although our patients experience intense discomfort at the height of the irradiation effect, the acute cystitis, proctitis, and enteritis subsided with little permanent injury to these structures. The opportunity of inspecting the pelvis in cases of endometrial carcinoma that have been irradiated similarly and then subjected to hysterectomy has revealed no significant injury to the pelvic viscera.

Radium therapy is carried on in conjunction with the x-ray therapy unless the condition of the cervix due to the malignancy is such that radium insertion would be difficult. Then the radium application is postponed until such a time as the tumor has regressed sufficiently to make less difficult the radium insertion. Fifty milligrams of radium filtered with 2 mm. brass and 3 mm. of para rubber is placed in the cervical canal for thirty hours. This dose is repeated at seven-day intervals for a total dose of 4,500 mg. hours. The placement of the radium in the capsule is so arranged as to irradiate the entire cervix from the internal os to the external os. The depth of the uterus is determined before each insertion and the length of the capsule adjusted accordingly.

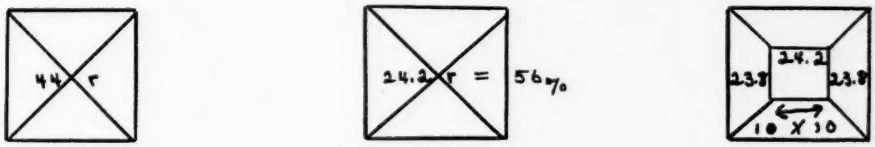

Fig. 2.—800 K.V.—10 Ma.—70 CM. F.S.D.
Filters Pb. 1.0 mm.
Sn. 1.56 mm.
Cu. 2.62 mm.
Al. 3.0 mm.
Extension Chamber 2.0 mm.
Size of Field 20 x 20 cm.
In Air—36 r

Surface with Backscatter 10 cm. depth 10 cm. depth

Further radium is occasionally used in the form of needles or a plaque against the cervix if regression has not been satisfactory. Such dosage is controlled by the size and location of the refractory area and in this group has never exceeded 1,500 mg. hours. If we accept the lethal radiation tissue dose for carcinomas of 5 to 7 E. D. as given by Wood and Prime[15] or 10 E. D. for squamous cell cancers and 2.5 E. D. for transitional cell cancers, as reported by Martin and Quimby,[5] we may assume that this combined radium and x-ray dose is adequate to destroy most squamous cell carcinomas for a distance of 3 cm. in all directions from the cervical canal. Sensitive cell types may be destroyed out to the limits of the bony pelvis. We rely entirely on x-ray therapy to destroy extension of the disease beyond the zone of effective radium rays. That certain cell types respond to this therapy is evidenced by survivals in clinical Groups III and IV and by the observation of Morton[7] that there were four times as many lymph gland metastases in nonirradiated patients. The five-year comparison of end results has influenced our decision not to increase the radium dose by applications against the cervix or to the fornices. Our low incidence of major complications, we believe, to be due to this fact.

TABLE IV

CLINICAL GROUP	I	II	III	IV	TOTAL
Total number admitted	11	37	70	48	166
Total five-year good end results	10	27	30	5	72
Percentage five-year good end results	90.90	72.70	42.85	10.43	43.37

Results

Table IV tabulates the five-year survivals in the cases treated by this technique. Seven cases in Group III have been lost to follow-up. The condition of the patient at the time of her last visit was such in each instance that we believe they all succumbed to the disease and we have, therefore, counted them as dead in determining our survival rate.

TABLE V

	1924-1929*					1933-1942				
CLINICAL GROUP	I	II	III	IV	TOTAL	I	II	III	IV	TOTAL
Total number admitted	23	36	100	116	275	11	37	70	48	166
Total five-year good end results	21	19	30	7	77	10	27	30	5	72
Percentage five-year good end results	91.3	52.78	30.0	6.04	28.0	90.90	72.70	42.85	10.43	43.37

*Schmitz, H.: Radiology 23: 548-550, 1934.

Table V compares this group of patients to a group previously reported. They received similar radium therapy but lower voltage x-ray. The improvement in the survival rate is, undoubtedly, due to the higher voltage x-ray in present usage.

TABLE VI. TEN-YEAR RESULTS, 1933 TO 1937

CLINICAL GROUP	I	II	III	IV	TOTAL
Total number	3	17	30	19	69
Total ten-year results	2	9	9	0	20
Percentage ten-year good end results	66.66	52.94	30.0	0	28.98

Sixty-nine of the 166 cases were treated before 1937 and can, therefore, be studied for a ten-year period. The death in the Group I case was due to coronary heart disease seven years after treatment. At autopsy no residual carcinoma was found. In Group II one patient died of metastases to the lungs six years after primary treatment. Autopsy failed to reveal residual carcinoma in her uterus. A second patient was lost track of after remaining free of symptoms for eight years. In Group III one patient suffered a fractured hip (not pathologic), and died of complications as a result of this seven years after her original therapy. Two other patients were lost track of in the sixth year having been free of demonstrable disease until this time. Two other patients died of recurrence in the fifth and ninth years, respectively. In Group IV one patient died of recurrence in the seventh year and two were lost to follow-up, one in the seventh year and the other nine years after therapy.

Discussion

The technique of radiation as described varies somewhat from the most widely accepted procedures because of the method of applying radium and x-rays and the dosages used. This has helped us to avoid the numerous complications of bowel, ureteral, and bladder injury described in many clinics and given by some as a most important reason for returning to surgical treatment. That the method is as effective is shown by the five-year relative cure rate of 43.37 per cent. Baschke and Cantril,[1] using x-rays of similar intensity administered through four 10 by 10 cm. fields and a radium dose of 4,000 mg.

hours through a cervical tandem and 4,000 mg. hours given through paracervical applicators, report a relative cure rate of 43 per cent, but warn against the use of the radium treatment during or following the course of roentgen therapy "as the rectal and intestinal complications are apparently more severe." Our experience with transvaginal x-ray therapy has been disappointing because of the difficulties associated with insertion of the rigid x-ray cone into an abnormal vaginal tube. We have, therefore, given up its use. It appears to us that radium and x-ray in safe dosage will destroy cancer within the region of the cervix in most instances (80 to 90 per cent). If the growth has extended into the paracervical areas, this cure rate drops to 52 to 56 per cent, the failures probably occurring in those cases with unrecognized lymph node metastases or extremely resistant cell type. It is in these instances that the Wertheim operation is indicated but present reports are not convincing enough to warrant its substitution in all Group I and II cases. Many of these patients would not meet the requirements for safe surgery and, therefore, the operative mortality rate would nullify the increased salvage. When the radium dose is increased the same situation results. The increase of complications is so marked that the salvage is not increased.

An attempt to follow our cases through the second five years was unsatisfactory although the absolute ten-year survival rate is 28.98 per cent. The age of these patients increases the death rate from all causes and it is more difficult to keep the patient coming to the clinic. That patients can have recurrences after five years is definitely shown in three cases that we know to have succumbed to recurrence of the disease after five years. That these losses could have been avoided by surgical measures employed after irradiation is questionable because the patients lost were in Groups II, III, and IV at the time of treatment and, therefore, not suitable for surgical procedures. In these cases the tumor cells are arrested for various lengths of time because of the inability of the cell to be active in the altered surroundings produced by the action of the x-rays and radium on the tissues. "If the tumor surroundings are so altered (fibrosclerosis) that the nutritive effect of this change cannot be overcome by the adaptability of tumor cells in successive generations, the tumor growth will finally stop and the cell strain will die (Clinical Cure)." (Windholtz[14].) However, if the tissues recover then the cell again becomes active and recurrence results.

The microscopic grading of tumors is an aid in predicting the response to therapy but not in determining the type of treatment indicated. A localized tumor irrespective of its cell type should be irradiated as in most instances it will respond satisfactorily. If it proves to be resistant to this form of treatment, surgery can be instituted and executed without increased difficulty. As the present time we are reserving the Wertheim hysterectomy for those cases proving to be resistant to our dosage of x-ray and radium as evidenced by persistence or recurrence of the lesion. In some instances where the extent of the disease has warranted such a radical procedure, we have combined the Wertheim hysterectomy with abdomino-perineal resection of the rectosigmoid. This permits thorough cleaning out of the entire pelvis. Such radical pro-

cedures are warranted, we believe, when radiation has failed. Surgery as extensive as this is relatively safe due to present-day methods. However, the end results will have to be studied before the procedure can be correctly evaluated.

The large number of recurrent cases in our series was due to the installation of higher voltage irradiation; many cases were referred because of failure of lower voltage x-ray so that higher voltage x-ray might be evaluated. Such material would not be referred to a surgical clinic and we, therefore, feel that these cases must be eliminated for comparative study. Of the 166 cases only 22.2 per cent were clearly operable (Groups I and II). However, according to Victor Bonney's[2] present indications for operation, many of our Group III cases would still fall into his operable group. The incidence of operability would still fall short of his 50 per cent. Our salvage in the Groups I and II cases was 70 per cent at the end of five years and 55 per cent for ten years. This is higher than for any comparable surgically treated group. Leclerc[4] had 59 per cent five-year survival with an operative mortality of 8.5 per cent in Group I (League of Nations) cases treated by Wertheim hysterectomy and Bonney 53 per cent in 300 cases in which there was no lymph node involvement. It is our decision, therefore, to continue treating all cases of cervix cancer with irradiation and to employ surgery for the conditions as stated.

Summary

One hundred sixty-six cases of primary carcinoma of the cervix admitted during the ten-year period of 1933 through 1942 are grouped clinically and graded microscopically.

The method of combined radium and x-ray therapy is described.

The five- and ten-year survivals have been determined and the advisability of combined surgical and radiological therapy is discussed.

The survival rate obtained in the Group I and II cases of this study are compared with reported series of surgically treated cases.

The evidence presented is in favor of continued radiological treatment of cervix cancer.

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Discussion

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—Although x-rays of as high voltage as 1,000, and even 2,000 kilovolts, are being used in some clinics, comparatively little information regarding the end results of this therapy in the treatment of carcinoma of the cervix is available. Leucutia claims 50 per cent five-year survivals with 400 kilovolts, as compared to 19 per cent with 200 kilovolts. Holmes and Schultz report 26 per cent five-year arrests, stages not noted.

The value of a report such as this is always enhanced by a description of the physical factors involved, as Dr. Schmitz has given us. His measurement of patients and calculation of dosage is similar to that employed by us at the Philadelphia General Hospital. Unless the dosage is determined precisely, one cannot administer x-ray therapy in adequate dosage, with the assurance of avoiding serious damage to normal tissues. It is quite apparent that since some of the rays are absorbed by the tissues through which they pass, a woman with a thick abdominal wall will require more external irradiation to administer the standard tumor dosage than would a patient with a thin abdominal wall. To avoid damage to the skin or vital organs, this may require the use of additional ports. It is my impression that we gynecologists have many times been derelict in failing to provide these data concerning the factors employed in our radium and x-ray therapy.

We also prefer and employ the Schmitz classification. I should like to emphasize Dr. Schmitz' point that in Stage IV cases x-ray therapy alone should be given. Following this, however, a number of lesions will become suitable for radium application.

In our clinic we use the four port technique, believing that thereby we avoid intensive irradiation of the bladder and rectum, as would be the case if one large anterior and one large posterior field were utilized. We credit this technique with the infrequency of serious damage to the intestinal tract in our experience. Del Regato employs the Trendelenburg position for his patients during treatment to avoid intestinal injury. It must also be remembered that with higher voltages a greater percentage of the irradiation passes, *unabsorbed,* through the tumor area to the normal tissues beyond. This so-called "exit dose" is great enough to be troublesome when it falls on the same area as the irradiation from the opposite field. It would seem that crossfire from three fields, whose paths do not overlap, might avoid some of the "exit dose" complications encountered in the use of the higher voltage.

Our experience with transvaginal high voltage therapy in carcinoma of the cervix has been so satisfactory in clearing up infection of the cervices, and in rendering the later intracervicouterine application of radium easier, that I was surprised to learn that Dr. Schmitz has discontinued this form of therapy. By utilizing cones of various sizes we have had no difficulty in centering the cone over the lesion. A periscope attached to the cone-adaptor enables us to confirm its position in relation to the lesion at any time. When cone therapy is used the lower voltages are considered more effectual and less likely to cause intestinal damage.

The end results here reported are so much superior to those obtained with lower voltages, as well as Dr. Schmitz' earlier series (Table V) where 200 kilovolts were used, that one cannot deny the superiority of 800 kilovolt x-ray therapy in conjunction with radium therapy, both in adequate dosage, in the treatment of carcinoma of the cervix.

How much the voltage can be increased advantageously is questionable. There would seem to be a limit to which the voltage or frequency can be increased without endangering the surrounding tissues, due to the high exit dose produced. Only the rays which are absorbed by the atoms of the tumor tissue affect the carcinoma. With higher frequencies the percentage of rays passing through the tumor unabsorbed is greater, thereby increasing the dosage to tissues around the tumor and to the skin.

Unless it is assumed, as claimed by Maisin and Estas, that rays of shorter wave lengths possess more energy and are more lethal to cancer cells than the same number of roentgens of lower voltage, it would seem from the point of view of the physicist that, with our present technical knowledge, voltages in excess of 800 or 1,000 kilovolts are of questionable advantage in the treatment of this disease.

Dr. Schmitz' report demonstrates:

1. The value of external roentgen therapy in addition to radium application in the treatment of cancer of the cervix.

2. The superior results of 800 kilovolt therapy over lower frequencies.

3. Irradiation should be administered to the limit of tolerance regardless of the histologic type or the size of the lesion.

4. Clinical grading is of greater prognostic value than cell typing.

5. Early diagnosis and treatment affect salvage more than any technical improvements that have yet been offered.

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—It is apparent from the physical properties of x-rays that, properly filtered, the so-called supervoltages, that is, voltages higher than the conventional 200 or 400 kilovolts, allow delivery of higher dosages to the depths of the pelvis without extreme skin injury. The aim in reporting series of patients such as this is to indicate the effectiveness or not of x-rays of this quality and amount delivered to the cancer-bearing areas. The figures just presented of five- and ten-year arrests are impressive. We are fortunate to have a report such as this from a group long experienced and interested in the treatment of cancer.

A point to be emphasized again in cancer reporting is that follow-up of patients with all its expense and difficulty is a very important thing since untraced patients are properly counted as dead of the disease. The author had good results in this series, notwithstanding having lost trace of seven patients of the 166, fortunately with enough final information about each to justify their inclusion as having succumbed to the disease. A few years ago in Cleveland, Dr. Lawrence Pomeroy attempted to establish some difference in results between four 200 kilovolt and 400 kilovolt machines used at different places in the city. He found it most discouraging to trust figures from public clinic groups with their shifting population and no efficient follow-up systems. Any group devoted to cancer therapy with a more or less personalized follow-up system can show much better results than others no matter what type of machine. If there is no other reason, adequate follow-up is an argument for specialized hospitals for the treatment of cancer, such as the author represents.

There is a personal sense of disappointment that the author has abandoned the vaginal cone method of therapy. From a limited experience it has been felt the development of this method might allow further reduction in radium dosage with consequent less reaction, immediate and remote, than now attends therapy of cancer of the cervix with radium and x-ray.

None of this series of patients was operated upon. The relegation of the Wertheim operation to recurrences and some patients not doing well with x-ray has interesting implications. Results of such operations will be looked for with interest in the future.

DR. GEORGE GRAY WARD, New York, N. Y.—Dr. Schmitz has shown the value of the very high voltage machine. At the Woman's Hospital we have only a 200 kilovolt machine.

The employment of the high voltage x-ray by the fractional technique in conjunction with the radium therapy has proved of definite value, and is generally employed. In the deep-seated lymphatic glands in the higher pelvis, however, the x-ray is not always effective. Hence the value of Taussig's procedure, or the extraperitoneal gland removal technique.

The results obtained by Behney and others using high voltage x-ray applied directly to the cervix with a vaginal cone apparatus promises much. It has not been in use a sufficient length of time as yet to evaluate it properly. We have been using this technique lately on a few cases.

The extent of the disease must be appraised to make a prophylactic probability. This is based on the clinical findings and does not permit us to know the actual extension of the carcinomatous involvement.

It is difficult to determine whether the parametrial infiltration is inflammatory or carcinomatous. Also it is not possible to demonstrate carcinomatous lymph nodes in the

higher pelvis by palpation. This impossibility makes doubtful the prognosis of a cure but justifies a therapeutic test by irradiation. The average cure rate by radiotherapy is about 25 per cent of all cases applying for treatment with a primary mortality of from 1 to 2 per cent. In a number of clinics this rate has recently been improved.

In the last report of the League of Nations on the results obtained by radiotherapy, which was collated in 1939, an analysis of 10,970 patients in all stages of the disease treated in European and American clinics showed a five-year cure rate of 26.7 per cent, and in the 1280 Stage I cases the cure rate was 56.1 per cent.

In the Woman's Hospital we have been treating carcinoma of the cervix with radiotherapy since 1919. Up to Jan. 1, 1947, we have seen approximately 1,045 cases. We have treated to 1940 inclusive and followed for five years or more 827 cases.

We have published six statistical reports of our results showing an improvement in the relative five-year cure rate as follows:—1925—23.6 per cent
1928—23.1 per cent
1930—25.5 per cent
1932—24.8 per cent
1934—25.28 per cent
1937—28.5 per cent.

Our seventh report recently compiled and not yet published is of cases seen from 1933 to 1940, of which there were 236 seen, 217 being treated, with a five-year absolute survival rate of 32.2 per cent, and a relative rate of 35 per cent.

In the League of Nations Stage I cases, the absolute rate was 57.1 per cent, and the relative rate 61.5 per cent.

In the League of Nations Stage II, III, and IV the survival rates were absolute 24.4 per cent, and relative 26.6 per cent.

The primary mortality was 1.28 per cent.

There were fifteen stump cases (following hysterectomy) in the 236, or 6.4 per cent, with a five-year salvage of 46.7 per cent.

I will close with repeating Professor Regaud's warning: "It is necessary to have much experience to obtain from this method of treatment all the good that it may give without the evil that it may do."

DR. SUBODH MITRA, Calcutta, India.—I thank Dr. Schmitz for assuring me that a high voltage treatment is very good in giving us a high rate of salvage. As a matter of fact, I have come to this country to study the work of radiotherapists and to acquire the best information which I can utilize in treating my cases with the million-volt x-ray apparatus.

Out of Dr. Schmitz' four hundred and odd cases he had a salvage of 65 out of his 132 primary cases. I doubt whether the results can be taken as an absolute rate.

Another point: Dr. Schmitz has given the operability rate at 22 per cent. Certainly it is too small a percentage. Mr. Bonney has 61 per cent operability rate and I have 57.6 per cent.

So far as radiation treatment is concerned, we know that there is an optimum dose. You cannot improve results by increasing the radiation; on the other hand, you may do much more harm. So there is a limitation for this irradiation treatment. You cannot do anything in relapse cases.

One point I should like to emphasize, that it is high time that the fight for the supremacy of irradiation over operation should come to an end.

As a gynecologist I find practically identical results with operation as with irradiation. It is very difficult to say which method is better, but perhaps the ideal would be to have two methods instead of one so that one or the other can be utilized.

DR. SCHMITZ (Closing).—I wish to thank Dr. Behney for bringing out the factor which we believe is responsible for our improved end results, and this is the fact that we are giving 12 per cent more radiation in the midpelvis and with the shorter, more rapidly traveling rays we are producing more destruction.

Relative to Dr. Faulkner's remarks about follow-up in these cases, it is one of the most important features of this type of work. We have a very definite plan of follow-up which time does not permit us to discuss at the present time.

Because of a fixed tube head on our 200 kilovolt apparatus we have had great difficulty in attempting transvaginal irradiation. Since having discussed the method with Dr. Behney I shall attempt it again. I can understand its value.

I am very much interested in Dr. Ward's remarks but I must disagree with the statement that irradiation has no effect on the tumor cells that have invaded the surrounding lymph nodes. Dr. Morton has shown in his studies that he found fewer invaded nodes in those cases treated with x-rays than in the cases that were not irradiated. Relative to the inflammatory invasion being mistaken for tumor invasion, that is true but we will err both ways so that in the end results it will be compensated for.

Original Communications

PELVIC DELIVERY FOLLOWING CESAREAN SECTION*

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IT IS readily understandable that in an era when cesarean section was reserved for cases of marked cephalopelvic disproportion there should arise the oft repeated dictum "Once a Cesarean, always a Cesarean." However, with the rapid progress in the development of aseptic, surgical technique and the introduction of potent chemotherapeutic agents, there has appeared a most gratifying decrease in the maternal mortality and morbidity accompanying the procedure, and an all too prevalent impression that the operation is both simple and safe. Consequently, it is not surprising to note the ever increasing incidence of the operation and the widening of its scope of application to such obstetric complications as placenta previa, premature separation of the normally implanted placenta, uterine inertia, and abnormal fetal presentation, not to dwell on the lengthy roll of questionable indications to be found in the literature. Regardless of what opinion one may possess toward the various indications, there nevertheless has come into being a not inconsiderable group of women, free from pelvic contraction and deformity, who have previously been subjected to cesarean section for some temporary consideration.

It is concerning this category of patient that we wish to dwell in some detail. The woman who has had a pregnancy terminated by hysterotomy and presents herself in a subsequent pregnancy creates a definite clinical problem and challenge. "To what degree is such a patient endangered by the presence of a scar in her uterus?" "What is the prospect for delivery through the natural birth canal in a succeeding pregnancy?" In spite of its significant practical consideration, the literature is meager concerning observations and study of pelvic delivery following cesarean section.

During the interval from Jan. 1, 1928, to Jan. 1, 1947, there have been effected at the Boston Lying-in Hospital one hundred seventy-seven deliveries through the natural birth passage in one hundred eighteen patients who had previously been subjected to cesarean section. Thirty of these women were delivered twice subsequent to hysterotomy, seven three times, two four times, one five times, and one six times, respectively.

It becomes readily evident from the above that during the past eleven years there has been a definite and steady increase in the number of pelvic

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deliveries in women having section scars. From Jan. 1, 1928, to Dec. 31, 1935, there were thirty-nine (22.0 per cent) such deliveries, whereas from Jan. 1, 1936, to Jan. 1, 1947, the total rose to one hundred thirty-eight (78.0 per cent). One might hastily attribute this rising incidence in more recent years to a corresponding increase in the frequency of cesarean section. A survey of the hospital statistics, however, demonstrates a distinct, even though slight, decline in the frequency of hysterotomy in the latter period.

TABLE I

Number of deliveries following cesarean section	1x	2x	3x	4x	5x	6x	Total
Number of patients	77	30	7	2	1	1	118
Total of deliveries	77	60	21	8	5	6	177

These deliveries were distributed over the period under investigation as follows:

TABLE II.

Year	1928	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	19 yrs.
No. of deliveries	4	0	6	2	7	12	6	2	11	17	10	11	11	19	13	14	9	13	10	177

This encouraging trend can be attributed to two major developments in clinic policy during the latter period; first, the adoption and wider employment of x-ray pelvimetry during the course of labor in cases of mild pelvic contraction and uterine inertia, enabling the more intelligent interpretation of progress during labor, and second, the greater consideration directed toward successful pelvic delivery following hysterotomy. During the past eleven years such deliveries alone have been responsible for a reduction of some 12.5 per cent in the total number of cesarean sections that would have resulted, had the presence of a uterine scar been considered an absolute indication for a repetition of the operation.

A large proportion of these patients (70 per cent) were delivered by forceps application after full dilatation of the cervix to avoid the expulsive stage, thereby minimizing the stress upon the uterine cicatrix.

TABLE III. TYPE OF DELIVERY

SPONTANEOUS	LOW FORCEPS	MID-FORCEPS	LOW FORCEPS FOLLOWING SCANZONI MANEUVER	LOW FORCEPS FOLLOWING MANUAL ROTATION	BREECH EXTRACTION
50-27.9%	112-62.6%	1	7	5	4

Sixty-eight (38 per cent) of these deliveries concluded the second pregnancy in patients whose first pregnancy was terminated by hysterotomy, so that for all practical purposes this group was subjected to what should be considered as a primiparous labor excluding the second stage. No disastrous sequellae were observed as a result of this policy, contrary to the opinion[1] that the long and tedious labor allegedly inherent in a primipara is to be avoided in the patient having had a previous cesarean section. The average duration of labor for the entire group was nine hours, twenty-five minutes. The average for deliveries through the primiparous cervix was fourteen hours, twenty minutes, the shortest such labor being four hours and the longest sixty hours. The multiparas averaged six hours, twenty-one minutes, the shortest labor being one-half hour, while

TABLE IV. DURATION OF LABOR

	PRIMIPAROUS CERVIX	MULTIPAROUS CERVIX	ENTIRE GROUP
Average duration of labor	14 hrs. 20 min.	6 hrs. 21 min.	9 hrs. 25 min.
Shortest labor	4 hrs.	30 min.	30 min.
Longest labor	60 hrs.	36 hrs.	60 hrs.

TABLE V. TYPE OF SECTION

	NO. OF DELIVERIES	NO. OF PATIENTS	
Classical	104 = 59%	66 = 56%	
Kerr	36 = 20%	24 = 20%	
Kroenig	10	9	
Latzko	7	3	a) Classical / Classical
Water's	2	2	
Vaginal hysterotomy	2	1	b) Classical / Classical
Multiple sections	4	4	
Unknown	12	10	c) Classical / Kerr
			d) Classical / Kerr
Total	177	118	

TABLE VI

SECTION PERFORMED AT	NO. OF DELIVERIES	NO. OF PATIENTS
Boston Lying-in Hospital	95 = 53.6%	60 = 50.8%
Other hospitals	82 = 46.4%	58 = 49.2%
Total	177	118

TABLE VII. CONVALESCENCE FOLLOWING SECTION

	NO. OF DELIVERIES	NO. OF PATIENTS
Afebrile	103 = 58.2%	72 = 61.0%
Febrile	42 = 23.7%	23 = 19.5%
Unknown	32 = 18.1%	23 = 19.5%
Total	177	118

the longest was of thirty-six hours' duration. Undoubtedly the reduction from the usually accepted statistics of primiparous and multiparous labors is to be attributed in some measure to the frequent elimination of the second stage of labor.

One hundred four (59 per cent) of the deliveries were in patients who had previously been subjected to the classical type of cesarean section, while thirty-six (20 per cent) occurred in women upon whom the low transverse (Kerr) type of section had been performed. Four patients, each of whom had experienced two previous hysterotomies, were each delivered once subsequently through the natural birth canal.

Approximately one-half of these patients had been operated upon in our own clinic, while an almost similar number were attended by their own physicians or at other clinics. For theoretical and practical considerations one would prefer to limit such deliveries to gravida who had been caesareanized in their own clinic for a temporary indication, and who had enjoyed an uncomplicated, afebrile convalescence. Even superficial inspection of the accompanying data will reveal that these criteria were not rigorously adhered to, fortunately, without development of any complications that could be attributed to such leniency.

As one would anticipate, the great proportion of these patients had been subjected to cesarean section for a temporary indication. The frequency of hemorrhage as an indication corresponds well with the high incidence of the classical type cesarean previously mentioned. This type of operation is the one employed in our clinic for cases of placenta previa and partial premature separation of the normally implanted placenta.

TABLE VIII. INDICATIONS FOR PREVIOUS CESAREAN SECTION

INDICATION	NO. OF DELIVERIES	NO. OF PATIENTS
Placenta previa	51 = 28.8%	34 = 28.8%
Premature separation of placenta	28 = 15.8%	16 = 13.5%
Uterine inertia	27 = 15.2%	19 = 16.1%
Cephalopelvic disproportion	26 = 14.7%	19 = 16.1%
Pre-eclampsia (severe)	12 = 6.8%	9 = 7.6%
Eclampsia	9 = 5.1%	4
Fetal distress	4	3
Prolapsed cord	3	2
Face presentation	2	2
Primiparous breech	1	1
Obstructing pelvic tumor	1	1
R.H.D.-M.S. and M.I. (early decomp.)	2	1
Hydrocephalus	3	1
Chorea	1	1
Varicosities of vulva	1	1
29-year-old primipara	3	1
Unknown	3	3
Total	177	118

Many of the cases of cephalopelvic disproportion were sectioned elsewhere or were delivered of infants considerably smaller than those for which they had been subjected to operation. It is most unfortunate that hydrocephalus, chorea, or elderly primiparity should ever appear in any roll of indications for cesarean section. If at the age of twenty-nine a woman is to be considered old, then certain physicians are soon to become quite unfamiliar with the mechanism, the ease, and the safety of pelvic delivery.

In more recent years it has become our policy to examine the uterine cavity immediately following the third stage of labor in every instance as a safeguard against any symptomless rupture that may have occurred in the uterine scar. The details of this aspect and the method employed in this clinic shall be discussed later.

TABLE IX

	NO. OF DELIVERIES	NO. OF PATIENTS
Exploration of uterine cavity	112 = 63.3%	83 = 70.3%
Not explored	65 = 36.7%	35 = 29.7%
Total	177	118

In spite of the fact that the uterus was explored manually in 112 cases only four patients in the entire group experienced a febrile convalescence, all of them mild in character. One patient whose uterus was not explored had a temperature of 100° to 101° F. during the first seven postpartum days, due to a mild sapremia. A second patient, who entered the hospital two days following

spontaneous rupture of the membranes, ran a temperature of 100° to 101° F. for five days following delivery as a result of sapremia. Cystitis was responsible for a temperature of 101° to 102° F. for a two-day interval in two remaining patients. This morbidity incidence is well within the zone of that for the general clinic population, a fact which is deserving of emphasis. When performed in accordance with well-prescribed aseptic technique, manual exploration of the uterus should have no effect upon the morbidity statistics.

The average hospital stay per patient for the group as a whole compared favorably with the general hospital population.

There was one maternal mortality in the series (0.56 per cent) occurring in 1932.

M. M., No. 6414, was a 25-year-old para iii, whose first pregnancy terminated in a normal spontaneous delivery. Two years later a classical hysterotomy was performed in our clinic because of painless, bright vaginal bleeding due to central placenta previa. Convalescence was uneventful. The present prenatal course was normal except for the development of mild pyelitis which cleared readily with conservative therapy, during the seventh month of gestation. Labor commenced spontaneously at term and progressed rapidly under pentobarbital medication. Four hours following admission to the hospital an easy low forceps delivery was performed under N_2O-O_2 ether anesthesia with the birth of a normal, active infant. The uterus was not explored. On recovering from the anesthesia the patient vomited a considerable amount of undigested food. She was well until twelve hours following delivery when she became markedly cyanotic, dyspneic, and apprehensive as a result of a "tightness" in her chest. The pulmonary condition became progressively worse with development of patchy areas of consolidation and bronchial breathing, together with rising pulse and respiratory rate. Exitus occurred forty hours following delivery and was attributed to aspiration pneumonitis. Postmortem examination was refused.

It is difficult to ascribe this disaster to any aspect peculiar to pelvic delivery following cesarean section. Such unfortunate circumstances might have resulted following any operative procedure, and more especially subsequent to a reiterative hysterotomy.

All but six of the infants in this series were discharged in good condition. Two were stillborn with extensive congenital deformities incompatible with life. A third was delivered macerated at thirty weeks' gestation. Another stillborn infant resulted from an easy multiparous breech delivery at term. Intrauterine asphyxia was attribued to the cord being tightly about the neck twice. A fifth stillbirth resulted at thirty-eight weeks' gestation in a multipara with mild pre-eclampsia who, on admission to the hospital in active labor, was bleeding considerably per vaginam. No fetal heart tones could be heard on admission. Labor progressed rapidly and she was delivered by low forceps at full dilatation of a stillborn 5-pound infant. The placenta showed marked premature separation and infarction. The sixth to be included in the infant mortality was a 7 pound, 15 ounce infant delivered normally at term after a short labor of an RH-negative mother. The infant expired at 24 hours of age of erythroblastosis.

It is only proper that the foregoing data be interpreted along with a consideration of whatever hazards may accompany attempts at delivery through the natural birth canal following previous cesarean section. The fundamental question, of course, revolves about the behavior of the uterine scar in subsequent pregnancies, whether it shall prove adequately firm to tolerate the distention of the uterus as pregnancy advances, and to withstand the stress of labor itself. The functional strength of the scar is intimately dependent upon the histology of wound healing in the uterus and the location of the incision. It is for this reason that a number of authors, during the past thirty years, have applied themselves especially to the anatomic study of these scars. There still appears to be considerable enthusiam existent in the controversy as to the exact nature of the reparative processes taking place in the healing of the uterine incision.

J. Whitridge Williams,[2] from a detailed study of uteri which had been subjected to one or more cesarean sections, noted that the old scar was invisible in most instances or could be identified at most by the presence of shallow vertical depressions over the external and internal surfaces of the anterior uterine wall. This observation has been confirmed frequently by Audebert,[3] Losee,[4] Eardley Holland,[5] and others. In more recent years, there have appeared reports of similar findings in studies directed to the scar in the lower uterine segment. Phaneuf[6] was unable to identify the cicatrix as such in forty-one repeat lower segment cesarean sections, whereas Fuchs[7] found it impossible to visualize the scar in thirty-three of forty-six cases upon which he performed a second cervical hysterotomy. Corroboratory observations have been made by Wetterwald[8] and DeLee, Nadelhoffer, and Greenhill.[9]

In 1895, von Baunfunwald, Shauta, and Brann[10] reported complete muscle regeneration in the scar following a cesarean section. More significant was Williams'[2] reiteration that microscopical examination of tissue removed from the site of the incision revealed complete absence of fibrous tissue in the uterine wall, demonstrating that the uterus, just as all other organs containing nonstriated muscle, heals by complete regeneration of muscle fibers and not by fibroblastic response. Two schools of thought have grown up around this issue: Williams,[2] Audebert,[3] Losee,[4] and Breitstein[11] have been convinced that in those cases where there has been perfect coaptation of the incised tissues, where the various layers have not been separated by blood clot, lochia, or serum, where there has been no infection, the incision heals by complete muscular regeneration in 80 per cent to 90 per cent of the cases. On the contrary, Couvelaire,[12] in 1909, in his report to the Societe d'Obstetrique de France, expressed doubt that the reparative processes could occur without fibrous tissue formation. Fruhinsholz,[13] Lauvray,[14] and Nicoletti,[15] concurred in this opinion. Schwartz and Paddock[16] appeared to have settled the issue in their exhaustive histological study on "The Cesarean Scar," concluding that muscle regeneration plays no important role in the healing of the scar, and that fibroblastic proliferation was practically normal. In a corroboratory study on a series of uteri from pregnant rabbits they[17] demonstrated the proliferation of fibroblasts along the line of incision entering the interstices between the adjacent muscle bundles. As the scar contracts, this becomes less perceptible, and it is difficult to demonstrate the line of the incision with the ordinary stains after a period of two weeks. It is this marked shrinking of the newly developed connective tissue and its branching penetration among the muscle fasciculae that make the cesarean scar so frequently invisible at a subsequent operation.

Mason and Williams,[18] in a series of experiments, carried out on pregnant guinea pigs and cats whose uteri were incised, noted that, after a reasonable convalescent period, with increasing stress exerted upon strips of the uterine muscle containing the scar, that rupture occurred not at the site of the old incision, but rather in the neighboring myometrium in every instance.

In 1886, Krukenberg[19] reported a series of twenty ruptures of the classical incision in a subsequent pregnancy, establishing an incidence of 50 per cent at a period, however, when it was the custom to return the unsutured uterus to the abdominal cavity, with little or no attempt to control hemorrhage. This is in marked contrast to the brilliant results that followed the adoption of the principles of suturing the incised uterus promulgated by Sänger[20] in his classic monograph in 1882. In the thirteen years that followed he was able to observe 500 consecutive women in a subsequent pregnancy without a single case of rupture of the cicatrix, an extraordinary accomplishment even today.[21] From 1882 to 1938 there have been reported a total of two hundred eight ruptures of the classical scar in a subsequent pregnancy. One may readily presume that reports of all cases have not found their way into the literature. The incidence of rupture following classical section varies from 2 per cent (Kerr[22]) to 6 per cent (Audebert[3]) with a generally accepted average of 4 per cent. Holland,[5] in his extensive follow-up of more than a thousand hysterotomies, demonstrated an incidence of 3.6 per cent. A recent survey by the McDowells[23] of 3,300 classical cesarean sections performed by the Potters of Buffalo, disclosed that fifty (1.5 per cent) had undergone spontaneous rupture in subsequent pregnancies with but a single mortality! With continued improvement in surgical technique and asepsis, it may be expected to note a progressive diminution in the frequency of ruptured scars.

Statistical surveys of rupture following low-flap cesarean sections may well reflect the results of surgical advances, in addition to the presence of the scar in the noncontractile portion of the uterus. Up to 1938, a total of thirty-eight[21] ruptures subsequent to cervical hysterotomy had been recorded in the literature. Wetterwald,[8] in 1926, reported an incidence of 0.28 per cent ruptures in a review of 3,600 pregnancies following previous low-flap section. Gellé[24] and Fournier[25] arrived at approximately the same figure, 0.25 per cent, or one-sixteenth of that following the classical type of operation.

From Jan. 1, 1928, to Jan. 1, 1947, we have witnessed eight cases of disruption of a cesarean scar in a subsequent pregnancy at the Boston Lying-in Hospital. These are recorded in some detail below.

Case 1.—E. C., No. 43997, 1929, was a 24-year-old para ii who had been subjected to a classical cesarean section for an unknown indication at another institution four years previously. She was attended by her own physician during this pregnancy. She began to experience bright vaginal bleeding, severe abdominal pain, and vomiting at thirty-seven weeks' gestation. She was then referred to the hospital in severe shock, with a classical picture of a ruptured uterus thirteen hours following the onset of symptoms. No apparent labor. Laparotomy was performed at once. The dead fetus and placenta were free in the general abdominal cavity amidst a large amount of blood and clot. The classical scar was found ruptured in its entire length. Supracervical hysterectomy with drainage was followed by a stormy convalescence, complicated by peritonitis, intestinal obstruction, and bronchopneumonia. The patient was discharged well on the fifty-eighth postoperative day. This case is a glaring illustration of grossly unintelligent management of a major obstetric problem prior to admission to the hospital.

CASE 2.—S. W., No. 3924, 1934, was a 36-year-old gravida vi, para iii, who had had a Kerr hysterotomy in 1928 following a test labor at another hospital. In 1932, a classical section was performed at still another institution. Thereafter, she miscarried three times at ten to sixteen weeks' gestation. When seen in our clinic for the first time she was registered for a third repeat hysterotomy and sterilization one week prior to her estimated date of confinement. Three days prior to the stipulated date of operation she entered the hospital, having been in active labor for four hours. Considerable time was required to locate the patient's spouse, whose signature was necessary for the sterilization procedure. In the one and one-half hours that elapsed the cervix became almost fully dilated and the head low when symptoms of uterine rupture developed acutely. Immediate laparotomy revealed multiple omental adhesions and rupture of the transverse scar with extension into the urinary bladder. The classical scar was found to be intact. Supracervical hysterectomy and reconstruction of the bladder with drainage were performed. The patient was discharged well on the twenty-sixth postoperative day after an afebrile convalescence. The infant succumbed four hours following delivery from atelectasis and intrauterine asphyxia.

CASE 3.—H. B., No. 17503, 1935, was a 30-year-old para iii whose first pregnancy was terminated by forceps delivery, in 1929, with birth of a normal infant weighing 7 lb., 11 ounces. In 1934, she was subjected to a classical hysterotomy for alleged disproportion at another institution. Convalescence was uneventful. While being followed in our clinic, arrangements were made for an elective, repeat section, one week prior to her estimated date of confinement. At thirty-seven and one-half weeks' gestation the patient was suddenly seized with acute abdominal pain and syncope. Laparotomy immediately on arrival at the hospital disclosed numerous adhesions about the old scar and the peritoneal cavity filled with liquid blood and large clots. A one and one-half inch rupture in the uterine scar was extended to permit delivery of a stillborn infant and the placenta which overlay the cicatrix. Scar was excised and uterine incision repaired. Patient was discharged on the seventeenth postoperative day following an afebrile convalescence.

CASE 4.—H. N., No. 13975, 1936, was a 24-year-old para ii whose first pregnancy was terminated by classical hysterotomy for severe pre-eclampsia in our clinic in 1934. She was discharged on the seventeenth day following an afebrile convalescence. Present pregnancy was uneventful until thirty-one weeks' gestation when she developed acute abdominal pain, tenderness over the abdominal scar, with frequency and urgency of urination. Laparotomy revealed complete disruption of the old scar. Nonviable twins and placenta were partially extruded through the rupture. Supracervical hysterectomy with drainage was followed by an afebrile convalescence and discharge on the sixteenth postoperative day.

CASE 5.—M. L., No. 21152, 1937, was a gravida v, para iv, whose second pregnancy was terminated by a Kerr hysterotomy in 1931, and a third pregnancy by classical cesarean section in 1933 because of a suspension and trachelorrhaphy performed one year after her first delivery (pelvic). Both cesareans were performed at another institution. She was registered for a third repeat section and sterilization to be performed one week prior to her estimated date of confinement. On the day prior to the stipulated date of operation, she developed acute abdominal pain. Immediate laparotomy disclosed a dead fetus and placenta free in the general peritoneal cavity, and disruption of the classical scar in its entirety, with extension to involve a portion of the lower transverse

cicatrix. Supravaginal hysterectomy with drainage was followed by an afebrile convalescence and discharge on the seventeenth postoperative day.

CASE 6.—M. B., No. 19663, 1938, was a 25-year-old para ii who in 1936 was subjected to a classical hysterotomy in our clinic because of cephalopelvic disproportion. While being re-examined at thirty-seven and one-half weeks gestation to determine the type of delivery she should have, the patient developed lower abdominal pain and a baseball-sized mass just below the umbilicus. The tumor mass became progressively larger while preparations were being made for operation. Laparotomy revealed rupture of the old scar in its entirety. The membranes were still intact. Following delivery of a living child, supracervical hysterectomy with drainage was performed. The patient was discharged on the nineteenth postoperative day after an uneventful convalescence.

CASE 7.—M. P., No. 19474, 1942, was a gravida iii, paraii, who suffered a fractured pelvis as a result of an automobile accident in 1932. Because of the resultant pelvic deformity an elective classical cesarean section was performed at the Boston Lying-in Hospital in 1936. Convalescence was uneventful and afebrile. The following year she was delivered precipitously of a 6-pound infant at another institution. In this third pregnancy it was elected to permit a test of labor. The patient entered the hospital in mild labor ten days prior to her estimated date of confinement. Following twelve hours of mild labor she suddenly developed severe suprapubic pain. Immediate laparotomy disclosed a dead fetus and placenta free in the general peritoneal cavity, and disruption of the previous classical scar in its entirety. Supracervical hysterectomy was followed by an afebrile convalescence and discharge on the seventeenth postoperative day.

CASE 8.—T. M., No. 38696, 1944, was a gravida ii, para i, whose first pregnancy was terminated by classical cesarean section for placenta previa two years previously at another hospital. X-rays revealed an ample, gynecoid pelvis. It was elected to permit a test of labor. At term the patient suddenly developed severe lower abdominal pain. No labor. On admission to the hospital shortly thereafter immediate laparotomy disclosed a rupture of the previous cesarean scar almost in its entirety. The membranes were still intact, an active infant in good condition was delivered through the rent in the uterus. Supracervical hysterectomy was followed by an afebrile convalescence. Mother and infant were discharged well on the seventeenth postoperative day.

Disruption of cesarean scars forms approximately 20 per cent[26] of all uterine ruptures. Though rupture of the uterus is to be considered among the most serious of all obstetric complications, the accompanying statistics disclose that the accident, when a cesarean scar is implicated, is not accompanied by nearly as formidable a maternal mortality as when it results spontaneously or following a traumatic procedure in the uterus free from a cicatrix. The mortality may be conservatively estimated to be in the vicinity of 10 per cent to 15 per cent under the guidance of good obstetric surveillance. The fetal mortality, however, ranges from 70 per cent to 100 per cent.

A sinister feature of rupture of cesarean scars is that the accident may occur at any period of gestation or labor. This adds to the difficulty, however forewarned by our knowledge of the risk to the patient, to protect her completely. Numerous reports of individual cases of spontaneous disruption of the cicatrix in the relatively early stages of gestation have appeared in the literature;

TABLE X. MATERNAL MORTALITY IN UTERINE RUPTURE

AUTHOR	PREVIOUS CESAREANS: CASES NO. OF	PREVIOUS CESAREANS: MATERNAL MORTALITY	NO PREVIOUS CESAREANS: NO. OF CASES	NO PREVIOUS CESAREANS: MATERNAL MORTALITY
Findley[27] 1916	59	18 – 30.5%		
Holland[5] 1921	97	28 - 28.9%		
Davis[28] 1927	24	3 - 12.5%	82	54 – 65.9%
Sacks[29] 1930			24	14 – 58.3%
Bey[30] 1932			110	56 %
Sheldon[31] 1936	7	1 – 14.3%	19	8 – 42.1%
Seley[32] 1937	3	0 – 0 %	9	1 – 11.1%
McNeile[33] 1938		20 %		90 %
Potters[23] 1939	51	1 – 2.0%		
Burkous[34] 1941	18	2 – 11.1%	27	15 – 55.6%
B.L.I. cases listed above	8	0 – 0 %		

Barnes (24 weeks),[39] Wilson (28 weeks),[40] Orrul (28 weeks),[41] Nicholson (28, 32, and 34 weeks),[42] Slevin (30 weeks),[43] and Ford (35 weeks).[44] The accompanying table illustrates that an appreciable number (26.1 per cent) of cesarean scars separate prior to the time when one would ordinarily elect to perform a repeat hysterotomy.

TABLE XI. STAGE OF PREGNANCY AT WHICH RUPTURE OCCURS

AUTHOR	WEEKS 28	29	30	31	32	33	34	35	36	37	38	40	PROPORTION OF CASES OCCURRING AT 38 WEEKS OR EARLIER
Findley[27]					6				2		3	42	11 – 20.8%
Holland[5]		1			11		1		14	2	4	53	33 – 37.2%
Singer & Marioton[37]					7							14	7 – 33.3%
Mariana[38]					7				12		5	111	24 – 17.8%
B.L.I. cases cited				1						1	2	4	4 – 50.0%
Total												224	79 26.1%

In our series of eight cases of ruptured cesarean scars detailed previously, but two such accidents occurred in patients who were selected for prospective delivery through the pelvis. Only one of these patients, however, experienced labor, the second suffering spontaneous rupture before the onset of uterine contractions. The remaining six disruptions occurred without labor prior to the appointed date of repeat hysterotomy, customarily performed one week prior to the expected date of confinement in this clinic. This group of cases reflects in a small way the facts frequently reported in the literature.

We shall not dwell upon the factors that encourage imperfection in the cesarean scar, nor attempt to explain the low incidence of rupture (0.25 per cent) among cervical sections as compared with the frequency (3 per cent to 4 per cent) in the classical type. However, when the uterine incision has been sutured carefully in accordance with well-established surgical principles, and when there has been no subsequent infection as characterized by foul lochia or a febrile convalescence, one may well expect the scar to be capable of withstanding the distention of the maturing pregnancy and the stress of labor itself. With attention directed to the perfect coaptation of the margins of the incision and to the avoidance of muscle infarction, bacterial invasion of the wound will be discouraged. Many have emphasized that placental implantation over the scar

predisposes to rupture. It may be this latter factor, together with its site in the noncontractile portion of the uterus, which accounts for the lower incidence of disruptions in cervical scars.

Because of the seriousness of this accident, such pregnancies, labors, and deliveries should be directed by well-trained obstetricians and conducted in maternity hospitals thoroughly equipped to cope with any obstetric complication. The most ideal results are to be expected when the patients are limited to those who have been subjected to a hysterotomy for a temporary indication in one's own clinic, and who are known to have enjoyed an uneventful, afebrile convalescence. As indicated previously, however, we were much more lenient in our selection of cases. The fruitful dividends that eventuate more than compensate the precautions necessary for the successful management of this group of cases.

These patients should be encouraged to seek prenatal care early in their subsequent pregnancies, at which time it is desirable to acquaint them with signs of rupture and to urge them to report promptly any suggestive symptoms. At the initial prenatal visit, or shortly thereafter, the patient's blood type should be determined. Such procedure will conserve valuable time should rupture of the uterine scar occur at any period of gestation, necessitating the prompt administration of blood to combat shock. Hospital blood banks have proved invaluable in just these exigencies.

As suggested by Dippel and Brown,[45] soft tissue roentgenograms of the anterior uterine wall in the last month of pregnancy might prove useful in determining the relative soundness of the myometrium in the region of a previous longitudinal cesarean wound. We have attempted to visualize the anterior wall thickness in a small series of patients previously delivered by cesarean section and found definite, irregular thinning of the anterior uterine wall in one instance. At the time of repeat hysterotomy, the scar proved to be defective as a result of attenuated fibrous tissue. Only positive findings of this nature would be of value, while negative observations would not preclude the absence of a weak cicatrix.

The patient must be impressed with the significance of entering the hospital at the very onset of labor, rupture of the membranes, or appearance of show. Only by uninterrupted, close observation during labor can the earliest signs and symptoms of impending rupture be detected. A compatible family donor should accompany the patient to the hospital with the intention of remaining in the waiting room throughout her labor and until the successful conclusion of delivery. This precaution must be observed, regardless of the associated inconvenience, unless the institution possesses some other reservoir of blood (blood bank). If labor progresses satisfactorily, one may anticipate a favorable termination, while the intervention of severe uterine inertia may be the factor to influence one to perform a repeat cesarean section. The use of pituitary preparations during such labors is mentioned, only to be unequivocally censured.

As mentioned earlier, it is our policy in these cases to eliminate the second stage of labor by effecting delivery by low forceps operation at full dilatation of the cervix. We are of the opinion that such conduct is beneficial in avoiding the rigorous stress of the expulsive stage. Intrauterine manipulations such as internal podalic version or difficult forceps operations invite traumatic rupture of the uterine scar.

Following delivery, the placenta is permitted to separate spontaneously. Oxytoxic preparations are avoided until after the cavity of the uterus has been explored. The administration of pituitary extract usually causes such vigorously sustained contraction of the myometrium that the accoucher may be unable to insert his hand into the uterine cavity to perform a satisfactory examination, or it may even conceal a small rent in the cicatrix. When the placenta has been expressed, the accoucher should don fresh sterile gown and gloves, while the perineum is prepared anew and redraped. The entire gloved hand is now placed within the uterine cavity to permit a careful, complete examination. It has been our experience that the greater portion of scars in the lower uterine segment are indistinguishable, whereas a furrow or cleft of varying depth can almost invariably be palpated underlying the classical type of scar. Manual exploration of the uterine cavity should be conducted in a systematic fashion so that small oblique ruptures will not escape detection. All portions of the uterus, including the fundus and the lower segment, must be palpated. The examining fingers are pressed firmly against the inner surface of the uterus by counter-pressure of the external hand, and are guided over all surfaces in four directions: from above, downward; from below, upward; from right to left; and from left to right. It is advisable to repeat the foregoing procedure a second time at the suspected site of the old cesarean scar. Only after the accoucher has convinced himself beyond any doubt of the integrity of the uterus may both the pituitary and ergot preparations be administered. There is, to be sure, a slight increase in the amount of blood loss associated with delivery as a result of the delayed use of the oxytocic principles.

From an analysis of our own cases and a review of the literature, we cannot but conclude that in properly selected cases that have been previously subjected to cesarean section for some temporary indication, attempts at pelvic delivery are to be encouraged, providing the foregoing precautions are observed. By pursuit of such a policy, one may anticipate not only a considerable curtailment in the frequency of cesarean section, but a gratifying reduction in the maternal mortality and morbidity, as well as a conservation of hospital days.

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THE ARREST OF ABNORMAL UTERINE BLEEDING WITH PITRESSIN TANNATE IN OIL

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ONE of the most difficult gynecologic accomplishments is the prompt stypsis of uterine bleeding without resort to emergency surgery.[7, 20] Such bleeding, when prolonged and profuse, hazards the patient's health, efficiency, and comfort. Uterine bleeding is, of course, a symptom and not a disease entity; and accurate diagnosis must always precede final, curative therapeusis. During the period of investigation, however, the quantity of blood lost may be so excessive that a temporary check of the flow may be indicated. Under these circumstances, any simple method which will accomplish this arrest of flow without obscuring subsequent diagnosis or doing harm to the patient is a very worth-while addition to our armamentarium.

The control of uterine bleeding by means of steroid hormones is often contraindicated in premenopausal and adolescent gynecologic patients.[8, 15, 19, 21] It is also necessary to stop blood loss in other patients in whom the diagnosis has already been established, or in whom so-called "functional uterine bleeding" tends to recur. In short, there are many types of patients in whose treatment we could use a safe, direct, inexpensive uterine hemostatic agent.

Since antiquity, countless medications have been used in the control of menometrorrhagia. Despite this fact we feel that it is appropriate to present our experience with another hemostatic agent in the hope that it may offer advantages over those presently in use.

Pitressin Tannate in Oil offers a new and physiologically sound approach to the prompt arrest of uterine bleeding.

Pitressin—the vasopressor fraction of the posterior pituitary—is a powerful stimulant to uterine contraction in the nonpregnant uterus. In this sense, it offers a mechanical tamponade to uterine bleeding. This is contrary to what we might expect in terms of the reactivity of the parturient uterus. On the other hand, Pitocin—the fraction which is oxytocic in late pregnancy and parturition—is without demonstrable action in the nongravid organ.[11, 13, 14] The nonpregnant uterus is known to respond clinically to pituitary extract during menstruation.[10] Actually, this oxytocic effect is due to the Pitressin fraction. Such a response is present at every phase of the menstrual cycle, but maximal contraction occurs just before, during, and immediately after menstruation.[11]

The response of the early pregnant uterus is weak to posterior pituitary fractions. But, the response to Pitressin becomes remarkably strong in incom-

plete abortion where the uterus has been sensitized, as it were, for expulsion of the fetus.[14]

Moehlig, in 1943,[12] was the first investigator to use pitressin tannate in oil in gynecology. His report, the only one in the literature, describes its use in ten cases. He employed 1 c.c. (5 pressor units) as an initial dose in the control of dysfunctional uterine bleeding. His patients "responded with cessation of flow within six to seventy-two hours following the first or second intramuscular injection of pitressin tannate in oil." Moehlig believed that smaller doses might be effectively hemostatic, but he actually used more than 1 c.c. (5 pressor units) *total* of the drug or more than one injection for the most of his patients.

In a preliminary series of thirteen patients, we administered 1.0 c.c. (5 pressor units) of Pitressin Tannate in Oil intramuscularly. This dose was repeated in forty-eight hours. The results were encouraging, since all patients responded favorably. Seven stopped bleeding completely, and six slackened markedly in forty-eight hours. However, it seemed desirable to eliminate a second injection. We wished to simplify the method and wished to obtain an even better check of bleeding—if this were possible. Therefore, in the series of 100 cases here reported, we administered a *single* dose of 2.0 c.c. (10 pressor units) of Pitressin Tannate in Oil intramuscularly to patients presenting all types of uterine bleeding. No subsequent injections of the drug were employed.

Material and Methods

One hundred consecutive gynecologic patients were treated with Pitressin Tannate in Oil for the control of uterine bleeding. The type of bleeding reported was in all cases prolonged, profuse, or irregular. No screening of patients was permitted in this study—save the elimination of suspected or known pelvic malignancy. Certain patients were pregnant, and abortion was the likely cause of the uterine bleeding. Cases of salpingitis, uterine tumor, ovarian cyst, uterine retroversion, etc., were grouped together. With these we included patients bleeding due to complications of pregnancy and cases of hormone imbalance or dysfunctional uterine bleeding—in order to attack the problem of arrest of uterine bleeding from a wide perspective.

Each patient received a complete physical and gynecologic examination. The blood pressure, pulse rate, and blood-urine findings were recorded. Medical or surgical consultation was obtained prior to gynecologic therapy with pitressin. An endometrial biopsy was secured and Pitressin Tannate in Oil was administered intramuscularly—provided there were no contraindications. The woman was seen again in two days and, when possible, the endometrial biopsy was repeated. A notation of the slackening of bleeding, side-effects, etc., was made. Each patient was required to return for re-examination after the next menstrual period or episode of uterine bleeding.

Many acute gynecologic problems were hospitalized. After ninety-six hours observation for stypsis, all patients received accepted medical or surgical treatment as indicated. In hormone imbalance or deficiency cases, supplementary or regulative endocrine therapy was effected.

Specimens secured at surgery were sectioned and pathologic data added to the facts obtained by the study of the previous endometrial biopsies. A three-month follow-up was attempted in all cases; basal body temperature charts, vaginal smears, and endometrial biopsies facilitated our studies.

Results

Table I presents a correlation of the endometrial findings with the clinical diagnoses. Table II presents the results obtained with a single dose of Pitressin Tannate in Oil in the various clinical conditions. Table III presents the results obtained as correlated with the type of endometrium present.

TABLE I. CLINICAL DIAGNOSIS AND ENDOMETRIAL TYPE IN CASES OF ABNORMAL UTERINE BLEEDING TREATED WITH PITRESSIN TANNATE IN OIL

	ENDOMETRIAL TYPE (BIOPSY)					
CLINICAL DIAGNOSIS	ENDOMETRIUM OF PREGNANCY WITH CHORIONIC VILLI	SECRETORY TYPE ENDOMETRIUM	PROLIFERATIVE TYPE ENDOMETRIUM	HYPERPLASIA OF ENDOMETRIUM	CASES	PER CENT
Normal pelvic examination		13	19	6	38	38
Pregnancy complications	7	13	2		22	22
Ovarian failure—natural menopause		1	5	1	7	7
Uterine myomas			6	1	7	7
Salpingitis, acute		3		3	6	6
Ovarian cyst		3	1	1	5	5
Ovarian failure—surgical			4		4	4
Salpingitis, chronic			1	1	2	2
Polyglandular dyscrasia			2		2	2
Pulmonary tuberculosis			1		1	1
Pelvic tuberculosis			1		1	1
Hyperthyroidism			1		1	1
Uterine retroversion		1			1	1
Acute respiratory infection			1		1	1
Endometritis (nonpregnant)			1		1	1
Appendicitis, Acute				1	1	1
Total	7	34	45	14	100	100

TABLE II. RESULTS OF TREATMENT WITH PITRESSIN TANNATE IN OIL AS RELATED TO CLINICAL DIAGNOSIS

CLINICAL DIAGNOSIS	BLEEDING STOPPED IN 48 HRS.	BLEEDING SLACKENED IN 48 HRS.	BLEEDING UNAFFECTED IN 48 HRS.	TOTAL CASES	PER CENT
Normal pelvic examination	19	14	5	38	38
Pregnancy complications	6	12	4	22	22
Ovarian failure, natural menopause	4	2	1	7	7
Uterine myomas	3	2	2	7	7
Salpingitis, acute	3	2	1	6	6
Ovarian cyst	2	1	2	5	5
Ovarian failure, surgical	2	2		4	4
Salpingitis, chronic		2		2	2
Polyglandular dyscrasia		2		2	2
Pulmonary tuberculosis	1			1	1
Pelvic tuberculosis	1			1	1
Hyperthyroidism	1			1	1
Uterine retroversion			1	1	1
Acute respiratory infection	1			1	1
Endometritis, nonpregnant	1			1	1
Appendicitis, acute	1			1	1
Total and per cent	45	39	16	100	100

TABLE III. RESULTS OF TREATMENT WITH PITRESSIN TANNATE IN OIL IN THE ARREST OF UTERINE BLEEDING AS CORRELATED WITH THE TYPE OF ENDOMETRIUM

ENDOMETRIAL TYPE	BLEEDING STOPPED IN 48 HRS.	BLEEDING SLACKENED IN 48 HRS.	BLEEDING UNAFFECTED IN 48 HRS.	TOTAL CASES AND PER CENT
Secretory	12	15	7	34
Proliferative	25	15	5	45
Hyperplasia	7	5	2	14
Endometrium of pregnancy with chorionic villi	1	4	2	7
Total and per cent	45	39	16	100

Of the 100 patients treated, 31 per cent stopped bleeding in twenty-four hours. Seventeen per cent more stopped bleeding in forty-eight hours. Thirty-nine per cent slackened appreciably with Pitressin Tannate therapy in forty-eight hours or less. Only 16 per cent failed to respond favorably to the drug in the two-day period. Therefore, 84 per cent of all cases of uterine bleeding were benefited to some degree.

The results of Pitressin Tannate therapy were encouraging in cases of:

1. "Functional uterine bleeding" (dysfunctional bleeding).
2. Ovarian failure (natural or post surgical).
3. Menometrorrhagia concomitant with or resulting from constitutional, intercurrent or nongynecologic disease.

Where overwhelming factors causing the uterine bleeding persisted, or where mechanical elements played a part, blood loss continued or was poorly checked. The results of pitressin tannate therapy were discouraging, therefore, in cases of:

1. Retained or adherent placental fragments.
2. Marked pelvic congestion (as with acute salpingitis, etc.)
3. Active or extreme hormone stimulation (haphazard hormone therapy, ovarian tumors or cysts).

It must be stressed that a single injection of Pitressin Tannate in Oil may not completely stop bleeding. Moreover, if bleeding does cease, it may be only for a limited time. Certain cases which showed definite slackening of flow continued to bleed after forty-eight hours and required curettage, abdominal surgery, hormone regulation, etc. This is not a fundamental criticism of the method. Our aim thus far has been to obtain prompt and effective, though admittedly temporary control of uterine bleeding with one injection of pitressin tannate in oil, a long-acting vasopressor-oxytocic preparation. No hemostatic will act indefinitely, and dosage requirements for that purpose are still to be accurately determined.

Curiously enough, one case of threatened abortion was not adversely affected by Pitressin Tannate in Oil therapy plus an endometrial biopsy. The tissue represented decidua only. This procedure followed inaccurate diagnosis on emergency admission. After a check of bleeding, the patient went to term and was delivered of a normal infant. One ectopic pregnancy—a tubal abortion—with a history of prolonged uterine bleeding abruptly ceased to flow following our therapy. The affected tube was removed electively. Generally speaking, however, Pitressin Tannate therapy did not check uterine bleeding adequately where the latter was caused by pregnancy or a complication of the puerperium; nor would the drug seem designed for this purpose. This is evidenced by the results obtained in the treatment of pregnancy complications as presented in Table IV.

Sixteen per cent of the entire 100 patients treated were failures. Bleeding either continued, or, in two instances, was more profuse. We are unable

TABLE IV. RESULTS OF TREATMENT WITH PITRESSIN TANNATE IN OIL IN THE ARREST OF UTERINE BLEEDING AS A COMPLICATION OF PREGNANCY

CLINICAL DIAGNOSIS	BLEEDING STOPPED IN 48 HRS.	BLEEDING SLACKENED IN 48 HRS.	BLEEDING UNAFFECTED IN 48 HRS.	CASES
Abortion—complete or ? incomplete	4	9	3	16
Postpartum bleeding—after term delivery	1	2		3
Ectopic pregnancy	1		1	2
Pregnancy, early not terminated		1		1
Total	6	12	4	23

TABLE V. CLINICAL DIAGNOSIS AND ENDOMETRIAL TYPE IN CASES FAILING TO RESPOND TO ARREST OF UTERINE BLEEDING WITH PITRESSIN TANNATE IN OIL

	ENDOMETRIAL TYPE (BIOPSY)				
CLINICAL DIAGNOSIS	PREGNANCY ENDOMETRIUM WITH CHORIONIC VILLI	SECRETORY TYPE ENDOMETRIUM	PROLIFERATIVE TYPE ENDOMETRIUM	HYPERPLASIA OF ENDOMETRIUM	CASES
Normal pelvic examination		2	2	1	5
Abortion, early	2	1			3
Ovarian cyst		1	1		2
Uterine myomata			1	1	2
Salpingitis, acute		1			1
Ovarian failure—natural menopause			1		1
Uterine retroversion		1			1
Ectopic pregnancy—ruptured		1			1
Total	2	7	5	2	16

to explain these failures, for it is not possible to make any correlation between the type of lesion and lack of effect of the drug. This fact is shown in Table V.

Toxic reactions to Pitressin Tannate in Oil, reported in the literature, include those occasionally noted with aqueous Pitressin:

1. Anaphylaxis
2. Local irritation
3. Intestinal cramps
4. Diarrhea
5. Headache
6. Palpitation
7. Pallor

These signs and symptoms are very rare with the oil preparation. With a long-acting drug of greater effective dosage, however, acute water retention may also be encountered.[12, 17] The signs and symptoms of this condition include:

1. Rapid weight gain
2. Persistent occipital and frontal headache
3. Listlessness and drowsiness
4. Blurring of vision

Acute water retention may occur in a susceptible individual with as little as 1 unit of pituitrin;[16] but such an occurrence is rare indeed. Alarming cardiac and renal symptoms secondary to vasoconstriction often followed the administration of Pitressin to animal and human subjects during early experimental work with this drug.[4, 6] However, we now know that the quantity of the drug used was either excessive, or the method of administration abrupt or by nonphysiologic routes. The safety of intramuscular administration—even to the hypertensive or cardiac patient—has been established with our lower dosage

level. There is no evidence that significant cardiovascular symptoms will occur in normal or cardiac patients when pitressin is administered—*if* it is not given beyond the *cumulative peak dose*. The principal warning of such a dose is abdominal pain and flatulence.[4] However, good judgment would suggest caution or avoidance of Pitressin therapy in severe nephritic, hypertensive, or cardiac patients. It may be hazardous in those threatened with decompensation or coronary occlusion[3] and in the patient with acute thyrotoxicosis.[18]

We have cautiously administered Pitressin Tannate in Oil to several patients with moderately severe hypertension, and have not noted any significant rise in blood pressure, headache, precordial pain, etc. Indeed, Pitressin Tannate in Oil has been used in the actual treatment of hypertension.[5] No patients with serious renal pathology have been treated in this series. In our entire series the reactions were few and mild; they are presented in Table VI.

TABLE VI. REACTIONS TO PITRESSIN TANNATE IN OIL IN THE ARREST OF ABNORMAL UTERINE BLEEDING
(100 Cases Treated)

COMPLAINT	CASES
Headache (frontal and/or occipital)	6
Oliguria (all less than 12 hours)	5
Edema (generalized)	1
Syncope (?—emotional)	1
Total	11

Discussion

With a long-acting preparation like Pitressin Tannate in Oil, there is a continuing release of the active pressor and antidiuretic principles. The usual relaxation of the musculature and vasculature which follows contraction only occurs after considerable time. The effective musculotropic action of Pitressin Tannate in Oil is probably three to six hours; the antidiuretic effect is about twelve to twenty-four hours.[9] In this series of cases, we have noted a definite, and at times abrupt restraint of bleeding as early as four hours after injection of Pitressin Tannate in Oil. Oliguria may accompany this diminution of bleeding. Within six to eight hours, there is generally more marked stypsis with some continued check of bleeding for forty-eight hours.

Effective contraction of the uterus together with primary vasoconstriction probably allows thrombosis in areas of rhexis, and either cessation or slackening of bleeding occurs. The actual mechanism is of course problematical, but this is a working thesis.

Hemostasis must be attributed to coincidence rather than to drug effect in cases of suppression of uterine bleeding eighteen to twenty-four hours *after* the injection of Pitressin Tannate in Oil. However, in the first twelve hours, once slackening occurs, suppression of bleeding does often continue for forty-eight hours. On the other hand, bleeding may persist if adverse mechanical or hormonal factors are involved.

Conclusions and Summary

1. Pitressin Tannate in Oil (2.0 c.c. or 10 pressor units) intramuscularly was employed as a single injection in 100 unselected gynecologic patients suffering from menometrorrhagia of all types, in an attempt to arrest uterine bleeding. Only cases of pelvic malignancy were excluded.

2. Thirty-one per cent of these patients ceased to bleed in twenty-four hours; 17 per cent more stopped bleeding in forty-eight hours. Thirty-five per cent slackened markedly in forty-eight hours, and only 16 per cent failed to note a check of bleeding. Unfortunately, a comparable control series would be difficult to obtain. It is probable, however, that cessation or slackening of bleeding from simple bed rest, delay, or natural healing processes would not occur so abruptly or in such a high percentage of patients. Moreover, these factors had already been operative in many of the patients of this series without appreciable amelioration of the bleeding.

3. Patients with gynecologic causes for uterine bleeding and those experiencing menometrorrhagia due to intercurrent or constitutional disease responded better to the styptic effect of Pitressin Tannate in Oil than patients with uterine bleeding due to complications of pregnancy—although all groups were benefited.

4. No serious toxic reactions or unusual side effects were noted.

5. Pitressin Tannate in Oil does not appear to alter the endometrial or hormonal pattern in menometrorrhagia. In that sense it is not a cure for the etiologic condition. It is postulated that the action is a mechanical one primarily on the endometrium and myometrium.

Pitressin Tannate in Oil is a water-insoluble preparation of Pitressin suspended in peanut oil. Each cubic centimeter contains sufficient hormone for activity equivalent to 5 pressor units of Pitressin. Supplied in 1-c.c. ampules.

We are indebted to Dr. E. A. Sharp, Director of the Department of Clinical Investigation of Parke, Davis and Company, for the grant of a generous quantity of Pitressin Tannate in Oil for clinical use.

The opinions or assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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THE EVALUATION OF THE RESULTS OF CARCINOMA OF THE CERVIX UTERI TREATED BY RADICAL VAGINAL OPERATION*

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DURING the Third International Radiological Congress in Paris (1931), where I submitted my five-year statistical end-result of carcinoma of the cervix uteri treated with radiation therapy, I was much impressed to find continental surgeons performing the radical vaginal operation in similar cases. On further inquiry, I found that by combining this operation with postoperative radiation, they obtained very satisfactory results. The rationale of the treatment of carcinoma of the cervix is still a controversial subject. Although the general trend of opinion is in favor of radiation therapy, the surgical treatment still occupies a definite place in its management. Moreover, some workers who were previously converts of radiation therapy are coming back to surgery supplemented by radiation therapy.

An analysis of world statistics shows that whatever method be followed (operation or radiation), the end-results are, for all practical purposes, the same in the hands of experts, with a small percentage of variation which may be a chance variation. The popularity of one method over the other depends not only upon the results obtained, but also upon the easy application of the method without harm to the patient. It is the general belief that radiation therapy is much easier to apply. There might be a bit of truth in it, but it is very difficult to check and control whether radiation therapy has been properly executed or not. Experts are of the opinion that "properly performed radium therapy is as difficult to learn as the operation itself." An irresponsible radiotherapist may carry on radiation therapy without being exposed to public criticism because there is much less chance of primary mortality. On the other hand, it has been remarked that the "operation for carcinoma of the cervix as performed by Halban, Adler, or Stoeckel, is much too formidable an operation for general use." My only remark is: does the defect lie in the method itself or in the true make-up of a gynecologic surgeon? Should a gynecologist be worth the name of a surgeon if he considers an important gynecologic operation formidable? I am more than conscious that everybody cannot be a Wertheim, a Bonney, or a Schauta, but can everybody be a Heyman? I believe that it is high time that the fight for the supremacy of one method over the other should come to an end. So far as cancer of the cervix is concerned, a gynecologist who wants to take it up as a life study must be a crack surgeon as well as a first class radiotherapist in order to work out by the process of evolution a more suitable technique in the

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near future, and thus to salvage more patients suffering from this fell disease. With this initiative, I started the radical vaginal operation in 1932, supplemented by postoperative radiation.

My Plea for Taking Up Radical Vaginal Operation

I believe that I have already made myself clear that, as much as I do not believe in the outstanding supremacy of one particular method of treatment, I do not at the same time decry any particular method as inferior to the other, provided it is efficiently carried out. I have taken up the radical vaginal operation instead of radical abdominal for the following reasons:

1. The primary mortality is much less. Of 151 patients operated upon, six patients died of operation, i.e., a primary mortality of 3.8 per cent as against an average of 14 per cent by the radical abdominal method.
2. Stocky, plump, and adipose patients can be more effectively tackled by the vaginal route.
3. Complications of the nature of ureterovaginal fistulae are much less frequent after vaginal operation than after the abdominal. Even in the hands of some experts, this complication may occur to the extent of 12.3 per cent after the Wertheim operation.
4. The end-results after Wertheim's radical abdominal operation and Schauta's radical vaginal operation are practically the same. In my series, there is 37.6 per cent relative cure rate, as against 39 per cent of Bonney's series.
5. The greatest handicap to the radical vaginal operation is that cancer-affected lymph glands cannot be removed. It has been authoritatively worked out by Bonney, Taussig, and others that there is glandular involvement in from 35 to 40 per cent of all patients presenting themselves for carcinoma of the cervix. Bonney claims that 23 per cent of the cases with gland involvement have passed through a five-year salvage, although the total relative cure rate is 39 per cent. Almost the same relative cure rate has been found in my series of radical vaginal operation without removal of glands. Heyman's series give still better results (absolute cure rate 33.1 per cent) without any surgical removal of glands. Schauta is of the opinion that radical removal of the glands is possibly only in occasional cases; because when the iliac glands, which may be removed, are involved, the aortic group of glands, which are not surgically approachable, are already carcinomatous. Some of the carcinomatous glands are bound to be overlooked because of their small size. Wertheim's opinion is that extirpation of the lymph glands can contribute nothing toward the improvement of end-results. The greater part of the lymphatic vessels infiltrated in a cervical carcinoma run with the uterine veins in the transverse cervical ligaments of Mackenrodt. When these lymphatic channels are infiltrated with carcinoma, cancer cells are well isolated from the rest of the body by the connective tissue sheath of the ligament. The spread of carcinoma is slow in this location because of the marked tissue pressure. Once the cancer cells pass beyond the connective tissue bundle of Mackenrodt, they extend into loose subserous connective tissue: the prospects are no longer good, even if the lesion may be found operable from the technical point of view. But, fortunately, cancer cells remain shut up in Mackenrodt's ligaments for a considerable time and then spread slowly. This slow permeation is the reason why cervical cancer is a relatively favorable type of tumor for operation.

The logical conclusion naturally follows that in operations for cervical carcinoma, the most radical possible excision of the parametrial and paravaginal tissue should be made including also a wide cuff of vagina.

The abdominal route was preferred originally because great hopes were placed in the removal of the glands: the excision of parametrial tissue was never considered as important as the removal of lymphatic glands.

6. The percentage of recurrence does not differ greatly after the two methods of operation, abdominal or vaginal. Kamniker, after making an extensive analysis of the materials of the first and second Universitats Frauen Klinik in Vienna, has found 55 per cent local and 30 per cent glandular recurrences in Schauta's operation, against 69 per cent local and 26 per cent glandular in Wertheim's operation.

7. The surgeon, expert in vaginal technique and thoroughly conversant with the surgical anatomy of the pelvis, can remove a greater amount of parametrial, paravaginal, paravesical, and pararectal connective tissue by the vaginal route with Schuchardt's incision than by the abdominal route. In my series, parametrium has been removed to the extent of about two and one-half inches from each side.

8. Lastly, the radical vaginal operation facilitates the introduction of radium in the parametrial tissue immediately or shortly after operation.

Technique (Special Points)

The carcinomatous growth is cauterized with surgical diathermy on the day previous to operation and dusted with "Cibazol" powder. Adrenalin (0.5 c.c.) with normal saline (70 to 100 c.c.) is next injected to the left side of perineum near the site of Schuchardt's incision.

Vaginal Cuff.—I make the vaginal cuff first when the vaginal outlet is very relaxed and the pelvis is one of gynecoid type, because by the time the cuff is made, adrenalin, already injected in the perineal tissue, will have its full effect. But if the vagina is narrow or the pelvis is one of anthropoid or android type, or if the growth is still a big one after cauterization, I make a Schuchardt's incision first. The making of the vaginal cuff is one of the most important steps of the operation. It is meant not only to cover the growth of the cervix, but to excise along with it quite a large amount of vagina and paravaginal connective tissue proportionate to the extent of the growth. The disadvantage is that the vagina becomes very small in some cases and inconveniences marital life, but recurrence of growth mostly occurs in the vaginal scar if sufficient vagina is not removed.

Schuchardt's Incision (Vagino-perineo-levatro incision).—This incision is generally made on the left side and it is better not to make the incision in one sweep, but in different layers. When the incision is properly made and a broad speculum inserted posteriorly, the approach to the internal genital organs with their attachments will be quite easy. The baldder and rectum are freely dissected out. Generally, this dissection is quite easy, but the difficulty arises as a result of any prior operation scar or too much scar tissue formation resulting from previous radium treatment, or due to marked infiltration of the base of the bladder extending from the cervix. Sometimes difficulties can be overcome by trying to free the bladder from the side instead of in the middle line. The bladder should be mobilized freely, not only in the middle line but also from the sides, and pushed beyond the uterovesical ligaments.

When the bladder has been freely dissected up to the uterovesical pouch and the uterovesical ligaments have been clearly exposed, the important stage of the operation, viz., the dissection of the uterine artery and ureter, begins. The ureter should be dissected freely and displaced laterally and upwards in order to make possible the removal of the maximal amount of the parametrial tissue. The dissection should be made by small steady and careful cuts with a pair of

scissors, and not merely pushed laterally without making any clear-cut demonstration of its topographical anatomy. Occasionally, the inferior vesical artery and vein may be cut during the process of dissection and should be ligatured.

After the vesical pillar has been further dissected up and laterally, the uterine vessels will be found near the junction of the cervix with the body of the uterus. As the uterine bundles are dissected and followed up laterally up to 1 to 2 centimeters, the deeper part of the ureter and its bend will be visible. This bend becomes more acute by pulling the uterus down.

When there is infiltration of the parametrial tissue the ureter is drawn closer to the uterus, and becomes adherent to its lateral aspect, and thus is apt to be injured even before the uterine bundle is made properly visible. It would be advisable for the beginner to cut through only those tissues which can be distinctly differentiated, and, as soon as the thicker strand of tissue is found extending from above downward, care must be taken of the ureter and an endeavor made to separate it from the uterine bundle, which courses rather transversely, by means of a closed pair of scissors. It is dangerous to make a blunt dissection with gauze, because if so, uterine bundles may be partly torn and the topographic representation will be altered. The ureter thus freed will appear as a typical whitish structure sometimes showing peristaltic contractions. The future dissection of the ureter and its separation from the uterine bundle will not be difficult.

The Radical Removal of the Parametrial Connective Tissue Is the Important Step of the Operation.—Extensive dissection and the steps of the operation so far followed are meant only to facilitate the radical removal of pelvic connective tissue. By opening the uterovesical pouch, the uterus is brought forward and separated with the appendages. The uterus now remains attached by the parametrial and paravaginal tissue, as well as by the uterosacral ligaments. First the rectum should be definitely separated from the uterosacral ligaments. To make the operation radical, it would be better to pull down the fundus by a strong pair of vulsellum forceps and the cervix by means of the traction thread on the right side, thus making the whole of the left parametrial tissue quite taut, and then divide with a pair of sharp scissors in one sweep as far laterally as possible, avoiding the rectum below and the ureter above. There might be a spurting middle hemorrhoidal artery or its branch which is easily ligatured. The amount of parametrial tissue removed on each side is to the extent of about two and one-half inches.

Postoperative Complications

Six patients died, the primary mortality being 3.8 per cent; three patients died of shock, one of pulmonary embolism on the fourteenth day, one of pneumonia, and one of staphylococcus septicemia.

The bladder was injured in six patients, of whom two required an operation for perfect recovery, whereas fistulae healed spontaneously in four other cases. In one case the ureteric wall was so much thinned out during dissection that it was almost on the point of rupturing, but by careful stitching of the outer coat nothing untoward happened. In three cases there was injury to the rectal wall, due to Schuchardt's incision, but it healed spontaneously. In 23 per cent of the patients the perineal incision did not unite by first intention, but later on healed by granulation. *Bacillus coli* infection is a common factor during the postoperative period to the extent of about 54 per cent. In four of my cases pyometra was present.

Statistical Analysis

For proper assaying of statistical results three things are essential, viz., operability rate, relative cure rate, and absolute cure rate. For the last twenty years I have been classifying my cases according to the League of Nations' formula and, since 1932, operation has been undertaken as a side chain to radiotherapy. Materials for operation were taken not only from Grades 1 and 2, but also from Grade 3. Thus, 42.6 per cent of Grade 1, 28 per cent of Grade 2, and 5 per cent of Grade 3 cases were operated upon, and the rest were treated with radiation therapy. Although all the clinical material was at my command, I did not insist on operation for all cases which were deemed operable. Patients were given a free choice, and operation was done only to willing patients, although I have found by careful scrutiny that 57.7 per cent of all cases could have been operated. I have operated on 151 patients, six of whom died of operation, the primary mortality being 3.8 per cent. The total number of patients operated upon between 1932 and 1940 is ninety-three. Five-year salvage cases totalled 35, i.e., a relative five-year cure rate of 37.6 per cent. The total number of patients operated upon between 1937 and 1940 is 40, of whom 16 patients were well after five years, thus yielding a relative five-year cure rate at 40 per cent. The total number of patients operated upon during 1932 to 1936 is 53, of which 19 were well after five years, and 13 after ten years, thus giving a relative cure rate of 36 and 24.5 per cent, respectively. When taken separately in different Grades, the five-year relative cure rates were 61.5 per cent of Grade 1, 44 per cent of Grade 2, and 15.6 per cent of Grade 3.

Against these figures and during the same period between 1932 and 1940, my five-year relative cure figures by radiotherapy are 66 per cent in Grade 1, 31.5 per cent in Grade 2, 12.6 per cent in Grade 3, and 2.3 per cent in Grade 4.

Unfortunately, I cannot give an absolute cure rate of my cases from 1932, as the patients cannot be grouped under one particular method of treatment. Result will certainly be vitiated if an attempt be made to find out an absolute cure rate of operation cases against the bulk of remaining cases who were treated by radiotherapy.

My results from radiation therapy from 1926 to 1932 are as follows: the relative five-year cure rates are a 53.4 per cent of Grade 1, 37.5 per cent of Grade 2, 9.4 per cent of Grade 3, 1.7 per cent of Grade 4. The absolute cure rate is at 12.9 per cent after five years and 9.4 per cent after ten years.

It is evident that the results of radiation are not so striking as those of operation. So far as radiation therapy is concerned, I am afraid my technique is perhaps not very accurate and precise. Besides, my hospital cannot afford to give free treatment to all patients, thereby sustaining a loss of the early cases. The patients are mostly poor and irresponsible. A good number of them (18.3 per cent) did not take the complete course of treatment, either because they could not afford it, or they thought they were cured in spite of repeated insistence to the contrary. Moreover, there being no arrangement for registration system, patients once changing their residence could hardly be traced. Lastly war, famine, flood, and communal disturbances have practically dislocated the civil life, thereby making difficult the following-up system. If I take a relative cure-rate of only those cases who have taken a complete course of treatment, the results will be 14.9 per cent, which stands comparable with the results of other workers.

Conclusions

In conclusion, I must admit that we have as yet no remedy for advanced cases. Operable cases yield satisfactory results up to a certain limit whatever method is followed, provided treatment be given efficiently and with meticu-

lous precision. It is only by the detection of early cases and centralization of patients in special cancer clinics that we can markedly improve our end-results and hence the right movement should be the education of lay public and special courses of cancer training for the general medical practitioners. I would like to quote a few lines from Bonney which I presume bespeaks the sincere aspiration of every gynecological surgeon: "So far as operation is concerned, apart from its effect on carcinoma of the cervix, it has been and still is a great educational factor in gynecology, and it has raised the reputation of gynecologic surgeons in the opinion of surgeons in general, for the procedure is the most difficult of all surgical procedures. It has taught us the anatomy of the pelvis in a way that no dissecting room preparations could possibly have taught, and it has enlarged the surgeon's vision, so that, though in the future we may quite possibly see it replaced by a treatment more efficient, its disappearance from the field of gynecology will not be an entire gain."

CARCINOMA OF THE CERVIX COMPLICATING PROCIDENTIA UTERI*

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THE following case is presented primarily as an addition to the rather small number of reported carcinomas of the prolapsed cervix. It may also be looked upon as one embodying a series of frustrations for the physician not unusual in the age group in which this disease most frequently occurs.

It concerns M. S., a white widow, aged 74 years. She was admitted to The Woman's Medical College Hospital of Pennsylvania on Aug. 10, 1946, with the chief complaint of "something coming down." Although she had had a sense of bearing down for thirty-one years since the birth of the last of her six children, she did not notice an actual protrusion until four years ago. For ten months the uterus had been prolapsed at all times and was not replacable. During this time the patient had almost no control of her bladder and there was a malodorous discharge, often bloody. She had lost forty pounds in the past year. Her menopause occurred at 48 years and was uneventful. She had been generally well, except for her chief complaint and gall-bladder trouble for the past two years.

On physical examination the positive findings included malnutrition, avitominosis, a systolic murmur over the precordium, blood pressure 95/60, and varices of both legs, especially the right. The white cell count was 14,600. A uterus the size of a small orange protruded through the vaginal orifice, and on the lower portion of this there was a fungating, friable, bleeding, irregular, red, foul-smelling mass twice the size of the uterus. The vaginal walls were leathery and the bladder fold not distinguishable. A biopsy of the cervix taken on August 12, revealed "an infiltrating, malignant tumor arising from stratified, squamous epithelium, with surface ulceration and hemorrhage." As many as seven mitotic figures could be identified in the high-power field. The pathologist's impression was grade 3 carcinoma of the cervix. Roentgen examination showed no evidence of metastases to lungs, thoracic cage, or shoulder girdle.

The treatment proposed consisted of x-ray, radium, and operation if indicated, in this order. Accordingly x-ray treatments were instituted and a total dosage of approximately 4,000 R.U. was given to the tumor. After this the patient developed ulcerations as large as the palm of the hand on the inner side of each thigh, probably due to an erythema, bathed in urine and discharge from the tumor. She was sent home, therefore, to return later for radium insertion.

She was readmitted, however, in a week for acute abdominal pain and jaundice. X-ray showed many small stones in the gall-bladder but no liver enlargement or evidence of skeletal metastases. After recovery from this attack she was again discharged. In four weeks the uterus was small enough to be replaced with difficulty, and a Menge pessary was inserted and left in for ten days. This was done in order that the patient could be out of bed (she had been unable to sit up while the mass protruded), that urinary leakage could be controlled, that the thigh ulcers could heal, that the uterus could be relieved of congestion, and that the general physical and mental condition could be improved.

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On readmission to the hospital, however, on Nov. 5, her general condition had definitely deteriorated and there was marked swelling of the right leg. Cystoscopic examination showed no bladder involvement, but vaginal examination showed a sloughing area deep in the posterior lip of the cervix extending back to the rectum. Therefore, the insertion of radium was abandoned. Subsequent to leaving the hospital the patient had two moderate vaginal hemorrhages and died after about six weeks. It is well known that the prognosis in carcinoma depends on the absence or presence of glandular involvement, and it seems unlikely that this patient was fortunate in this respect, even when first seen.

The second case occurred in the same hospital in 1931, and concerns a white woman, aged 47 years, gravida viii. She had had some prolapse for thirteen years following her last delivery, and procidentia for two years. The cervix showed an ulceration from which the biopsy was diagnosed, "squamous cell carcinoma," 4,800 mg. hours of radium were used, and three months later a vaginal hysterectomy was done. Seven years later the patient returned because of a recurrence in the vaginal vault for which she was given more radium. She is still attending the Follow-up Clinic.

These two cases of carcinomas of the cervix, complicating procidentia, were the only ones found in the years between 1931 and 1946 in the records of the Woman's Medical College Hospital, although during these same years there were 274 admissions for carcinomas of the cervix. At The Woman's Hospital of Philadelphia there were no cases of the type we are considering and 132 cases of cervical malignancy during the same years.

In reviewing the literature on this subject of carcinoma of the prolapsed cervix, the matter of incidence is very striking. It has been estimated in the United States yearly for the past twenty-five years that approximately 26,000 women have died of cancer of the uterus, over 80 per cent of them of cancer of the cervix. It has also been estimated that 4 per cent of erosions of the cervix develop carcinoma, first the one and then the other being based upon chronic irritation.

What are the statistics of cancer with procidentia where the cervix is especially subject to such irritation? In 1935, Brady summarized the literature, and I use this summary in several of the following references. In 1882 Fritsch said that the two conditions did not occur together. In 1893 Pontow collected 29 cases. Cullen at Johns Hopkins saw only one case, and Martzloff of the same institution reported in 1923 no cases to be found in that Hospital's statistics. Haegler at the second Frauenklinik in Vienna found five cases in 11,045 women, at the same time reporting the incidence of cancer of the cervix in women without procidentia as 7.2 per cent.

In 1930 a questionnaire sent to leading American gynecologists revealed the fact that 52.3 per cent had never seen a case, and another 27 per cent had seen only one. In 1931, Delvaux wrote to Hartman of Paris, Schroeder of Kiel, and Sellheim of Leipzig. These eminent gynecologists had seen no such cases. Smith, Graves, and Pemberton, after careful microscopic study, found one case in 683 prolapsed uteri. On the other hand, Emmert and Taussig in 1934 reported four cases observed in ten cases of procidentia. By 1943, seventy-eight cases were collected from the literature.

What explanation can be given by those who consider it a rare combination, as to the cause of its rarity? As Graves said, "It seems remarkable that the prolapsed uterus seems almost immune to cancer, despite the irritation, hypertrophy, impaired circulation, and infection which predisposes to squamous cell cancer in the normally located cervix." The chief theory advanced is that cornification of the epithelium in prolapse raises the resistance to cancer.

Emmert and Taussig challenge this by reference to the frequency of cancer of the lower lip of the face, and to their series of four carcinomas in ten cases of procidentia. They claim that "because it occurs in elderly women (50 per cent are over 60 years of age), in atrophic tissues, and where lymphatics are stretched and somewhat occluded, it is not very active;" and insist that more cases would be found if more decubitus ulcers were sectioned. One might answer by referring to the usual rapid healing of such ulcers before operation is undertaken, which healing in itself rules out malignancy. The question remains for future settlement.

As to treatment, although there is great temptation to do an early vaginal hysterectomy, this is not at present the accepted treatment, except in very early cases, any more than it is the accepted treatment of cervical cancer inside the vagina. Because of the presence of infection x-ray should be used first. This gives a uniform distribution of radiation, combats infection, and shrinks the tumor. Radium can then properly be used after replacement of the uterus, without the danger of severe pelvic infection and septicemia. It is interesting to note that subsequent operation is frequently unnecessary, although the exact mechanism by which the procidentia is relieved or cured is not known, unless it can be explained by the shrinkage of the supporting structures and reduction of the volume of the uterus.

In conclusion, it may be reiterated that the chief interest in this subject of carcinoma of the completely prolapsed cervix lies in its seeming rarity, and suggests the need for more detailed study of decubitus ulcers to prove whether or not that rarity is real. Certainly the preponderance of evidence points to a true scarcity, and arouses interest in an adequate explanation of such an arresting apparent paradox.

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Discussion

DR. GEORGE A. HAHN.—At the Oncologic Hospital since 1929 we have had about three hundred cases of carcinoma of the cervix, but no cases associated with procidentia. There was one patient who had been treated elsewhere; she had a Watkin's interposition performed because of moderate pelvic relaxation without complete prolapse, and at biopsy carcinoma of the cervix was found. She has since been treated and has remained well for four years. At Jefferson about 600 patients with primary carcinoma of the cervix have been treated on the ward service since 1920, and of that number there have been two cases with associated procidentia. The first of these patients was seen in January, 1933, with a prolapse of nineteen years' duration. Because of edema and the extent of the carcinoma the prolapsed organ could not be replaced within the vaginal orifice. X-ray treatment was given and the uterus regressed within the introitus. However, the carcinoma continued to advance and the patient died two months later. This case was reported by Dr. Scheffey in

the August, 1934, issue of AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.'' The second patient was treated at Jefferson Hospital in 1942 because of a group 2 Schmitz' carcinoma. There was a third degree cystocele and a rectocele. The patient was treated with deep x-ray therapy, and a few months later received local radium to a total of 4,400 mg./hr. It was interesting in going over the notes that in December, 1942, after radium had been given in July, that the prolapse was no longer apparent. In November of this year there was no prolapse present, but there was a small symptomless cystocele. The patient described herself as well in every respect.

Two additional cases were noted at Jefferson. One was a patient of Dr. David Farell, a group 1 lesion. She was treated with deep x-ray therapy followed by radium. The patient had a cystocele with procidentia and a third degree rectocele. This case was treated two and one-half years ago, and at the present time there is no prolapse and no apparent rectocele and a small cystocele. Her only complaint is occasional stress incontinence. This patient was not told of her malignancy, but thinks that the local radium and x-ray were given to cure her prolapse. Dr. Scheffey has asked me to present a case which he treated three years ago for procidentia with carcinoma of the cervix. The patient was given deep x-ray therapy and radium with regression of the prolapse. Dr. Scheffey felt this might be a patient suitable for Meigs-Wertheim type of radical complete hysterectomy. However, it was impossible to isolate adequately the ureters. In fact, dissection throughout was extremely difficult. The usual complete hysterectomy was done, and the patient returned to her room. Her convalescence was complicated by an unusual amount of sloughing in the vaginal vault. One year later the patient felt well, but there was still an ulcer 1½ cm. in diameter in the vault.

Dr. Ashton has mentioned the theories in regard to the rarity of procidentia associated with carcinoma of the cervix, and the need for the further study of cervical decubitus ulcers to see if the rarity is real or apparent. I would like to emphasize irradiation in the treatment of cervical cancer, whether associated with procidentia or not. After having reviewed these cases I was quite struck with the results of x-ray therapy in the correction of the associated prolapse, and I might even recommend that it be used electively to treat prolapse of the uterus.

In answer to Dr. Philip F. Williams' question concerning the ages of the patients; Dr. Farell's case was 54 years of age. The first ward case at Jefferson was 56 years of age. The second ward case was 66 years, and the private case of Dr. Scheffey's was 68 years.

A COMPARISON OF THE ACCURACY IN DIAGNOSIS OF THE VAGINAL SMEAR AND THE BIOPSY IN CARCINOMA OF THE CERVIX

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UNTIL recently the only accepted procedure in establishing a diagnosis of cervical malignancy was by the standard biopsy technique. However, the demonstration by Papanicolaou[1] in 1941 that uterine carcinomas cast off cells into the vagina which could be recognized as malignant in a high percentage of cases introduced a cytologic method of diagnosis as a supplement to the histologic examination. In 1943 Meigs et al[2] confirmed the diagnostic accuracy of the vaginal smear, and since that time many reports[3-7] have emphasized both the value and accuracy of the cytologic approach to the diagnosis of uterine cancer.

During the past four years over 5,000 vaginal smears from 3,800 cases have been examined at the Vincent Memorial Laboratory. The diagnoses obtained by these smears in relation to the final histologic reports have been analyzed elsewhere.[2, 8, 9] It is the intention of this paper to examine the accuracy of the cytologic and histologic methods by a comparison of the initial vaginal smear and the initial cervical biopsy in proved cases of cancer of the cervix. An attempt has been made to analyze the reasons for failures in both methods.

Material

It was felt that a fair evaluation of the biopsy and vaginal smear methods could be obtained by limiting the cases studied to those with primary epidermoid carcinoma of the cervix. In any series of uterine malignancies the surgeon should have the best chance in this group of recognizing and sampling the areas under suspicion. Only cases that had both biopsy and vaginal smear before radiation have been included. Only those in which both the biopsy specimen and the vaginal smear were available for review were used. Since 1942, when the Vincent Memorial Laboratory started to examine vaginal smears, until Dec. 31, 1946, there have been 228 epidermoid cervical carcinomas studied by this method. Forty-seven of these were omitted from this group because they were recurrent cases, had had previous radiation, or the biopsy specimen was taken at another hospital and was not available. There were, therefore, 181 cases that could be included in this study group.

Results

In 148 of these 181 cases, or 82 per cent, both the first vaginal smear and the first cervical biopsy were positive for cancer. There were sixteen false negative biopsies and fourteen false negative smears: in addition to these there were three cases in which both methods failed.

There were in all 19 cases, or 10.5 per cent, in which the first biopsy was negative. These errors in the biopsy method were carefully reviewed. The

diagnosis in one case was changed to carcinoma and four others were interpreted as suspicious. The remaining fourteen were still considered to be negative. The reasons for failure of the biopsy method are three. First, the majority occur because the surgeon did not choose the right area to biopsy. Some early cancers are grossly undetectable, and even with Schiller's iodine and the colposcope it may be impossible to locate the region involved in such tumors. Second, there are occasional errors due to misinterpretation of the specimen submitted. However, it is important to point out that the recognition of early structural changes pathognomonic of preinvasive cancer are recognized more often at the present time than they have been in the past. Smith and Pemberton,[10] Taylor,[11] and others, on reviewing cervical biopsies taken from three to eight years before, have found a number in which they have felt justified in reversing a previous negative report. Lesions now diagnosed unquestionably malignant may have been previously called benign. The third reason for errors in the biopsy method is that occasionally tissue must be considered "insufficient" for diagnosis. This usually occurs when no cervical epithelium is included on the slide. A cervical biopsy is at best a small piece of tissue which after fixation is difficult to orient in the paraffin block. Unless sections are made at right angles to the surface, all the epithelium may be shaved off and discarded with the initial segments of the paraffin ribbon. Davis,[12] in 1932, reported that 25 per cent of cervical biopsies failed to show any epithelium, and thus had to be reported as inadequate.

Of the 181 cases of epidermoid carcinoma, there were seventeen, or 9.4 per cent, in which the first vaginal smear was reported negative (Table I). These "negative" smears were reviewed carefully, and eight showed cancer cells on review. The reasons for failure in the vaginal smear method are three. Occasionally a tumor will not desquamate cells into the vagina. In this instance a negative diagnosis will be made although the patient may have uterine cancer. Second, cancer cells may have been present on the slide but not seen at the first examination. Every field of the slide must be covered or in certain cases malignant cells will be missed. Third, malignant cells may be misinterpreted as benign. It is obvious that an error of this kind will occur in any new method, but with more knowledge concerning the individual characteristics of malignant cells there should be a reduction in these mistakes.

TABLE I. PRIMARY EPIDERMOID CARCINOMA OF CERVIX, 181 CASES

	FIRST SMEAR REPORT	FIRST BIOPSY REPORT	TOTAL NUMBER	TOTAL PER CENT
Both methods right	+	+	148	81.7
False negative biopsy	+	−	16	8.8
False negative smear	−	+	14	7.7
Both methods wrong	−	−	3	1.7
			181	100

It is important to point out that although the first biopsy report was negative in 10 per cent of the cases and the first vaginal smear report negative in 9 per cent, there was only a 1.7 per cent error in initial diagnosis when the results of both methods were combined. This indicates that each method is complementary to the other. One should not be used to the exclusion of the other; together, they serve as checks upon one another. Whereas the biopsy makes the excised tissue alone available for study, the vaginal discharge contains examples of cells cast off from the whole of the epithelium of the cervix and uterus. This particular attribute of the vaginal smear suggests that it is of special value in those cases where the cancer is small or hidden from view

TABLE II. ONE HUNDRED EIGHTY-ONE EPIDERMOID CANCERS OF THE CERVIX
INITIAL STAGE OF THE DISEASE MISSED BY FIRST DIAGNOSTIC TEST*

	STAGE 0	STAGE I	STAGE II	STAGE III	STAGE IV
17 Negative smears	2	6	4	4	1
19 Negative pathologic reports	8	7	3	0	1

*The three cases initially missed by both smear and pathology are included in both the negative smear and pathology groups in this chart.

TABLE III. ONE HUNDRED EIGHTY-ONE EPIDERMOID CANCERS OF THE CERVIX, 17 CASES IN WHICH THE FIRST VAGINAL SMEAR WAS NEGATIVE*

NUBMER	SMEAR DATE AND REPORT	INITIAL STAGE	PATHOLOGY			SMEAR REVIEWED
			DATE	OPERATION	REPORT	
TC 187	7/10/43 negative	II	7/10/43	Biopsy	Epidermoid Ca	No Ca found
TC 262	1/31/44 negative	I	1/15/44	Biopsy	Epidermoid Ca	No Ca found
TC 229	5/5/44	I	5/ 2/42	Biopsy	Acute inflammation	Mistake; Ca present
			3/ 8/44	Hysterectomy	Epidermoid Ca Grade III	
M 414	6/23/44 negative	0	7/15/44	Biopsy	Chronic cervicitis	Mistake; Ca present
			7/17/44	Hysterectomy	Ca in situ	
TC 614	8/5/44 negative	0	8/ 7/44	Biopsy	Chronic cervicitis	No Ca found
			8/12/44	Hysterectomy	Ca in situ	
TC 984	3/15/45 negative	I	3/18/45	Biopsy	Epidermoid Ca Grade II	Mistake; Ca present
M 733	8/2/45 negative	II	8/13/45	Biopsy	Epidermoid Ca Grade II	Mistake; Ca present
M 875	8/29/45 negative	III	8/29/45	Biopsy	Epidermoid Ca Grade II	No Ca found
M 885	9/17/45 negative	I	9/17/45	Biopsy	Epidermoid Ca Grade III	Mistake; Ca found
TC 1387	10/20/45 negative	I	10/20/45	Biopsy	Epidermoid Ca Grade III	No Ca found
TC 1452	11/19/45 negative	IV	11/19/45	Biopsy	Epidermoid Ca Grade III	No Ca found
TC 1532	1/4/46 negative	III	1/ 7/46	Hysterectomy	Epidermoid Ca Grade III	Mistake; Ca present
TC 1774	4/1/46 negative	II	4/ 4/46	Biopsy	Epidermoid Ca Grade III	Mistake; Ca present
M 1197	4/1/46 negative	I	4/16/46	Cervicectomy	Early invasive Epidermoid Ca	No Ca found
M 1291	5/13//46 negative	II	5/13/46	Biopsy	Epidermoid Ca Grade III	Mistake; Ca present
TC 1993	6/26/46 negative	III	6/27/46	Biopsy	Epidermoid Ca Grade III	No Ca found
TC 2269	II/6/46 negative	III	11/ 6/46	Biopsy	Epidermoid Ca Grade II	No Ca found

*Includes the three cases in which the first biopsy was also negative for cancer.

within the external os, the very cases that give the surgeon little indication of likely areas to biopsy, and thus the particular ones in which the biopsy is most likely not to include malignant tissue. On the other hand, in those cases in which cancer cells fail to desquamate into the vagina and therefore the vaginal smear is negative, the biopsy may often give a positive diagnosis.

It is of particular importance to note which method proved to be the more reliable in diagnosing early lesions. According to the League of Nations Classification, Stage I applies to an early cancer completely confined to the cervix. We have further differentiated this group by classifying the preinvasive type of cancer (carcinoma-in-situ) as Stage 0. Chart II compares the

TABLE IV. ONE HUNDRED EIGHTY-ONE EPIDERMOID CANCERS OF THE CERVIX, 19 CASES IN WHICH THE FIRST PATHOLOGIC REPORT WAS NEGATIVE FOR MALIGNANCY*

NUMBER	SMEAR DATE AND REPORT	INITIAL STAGE	PATHOLOGY			PATHOLOGY REVIEWED
			DATE	OPERATION	REPORT	
TC 229	5/5/44 negative	I	5/ 2/42	Biopsy	Acute inflammation	Suspicious
			3/ 8/44	Hysterectomy	Epidermoid Ca Grade III	
M 149	1/18/43 positive	0	12/ 4/42	Biopsy	Chronic cervicitis	Negative
			1/ 3/43	Hysterectomy	Cancer in situ	
M 116	11/18/43 positive	I	11/18/43	Biopsy	Cervical polyp	Negative
			12/ 8/43	Biopsy	Epidermoid Ca Grade III	
TC 61	2/4/43 positive	II	1/27/43	Biopsy	Leukoplakia	Atypical leukoplakia
			2/18/43	Hysterectomy	Epidermoid Ca Grade I	
TC 417	4/29/44 positive	I	4/29/44	Biopsy	Acute and chronic inflammation	Negative
			5/13/44	Hysterectomy	Epidermoid Ca Grade III	
TC 440	5/6/44 positive	I	5/ 6/44	Biopsy	Acute inflammation	Negative
			5/19/44	Hysterectomy	Epidermoid Ca Grade I	
M 414	6/23/44 negative	0	7/15/44	Biopsy	Chronic cervicitis	Negative
			7/17/44	Hysterectomy	Cancer in situ	
TC 614	8/5/44 negative	0	8/ 7/44	Biopsy	Chronic cervicitis	Negative
			8/12/44	Hysterectomy	Cancer in situ	
TC II94	6/30/45 positive	I	7/14/45	Biopsy	Chronic cervicitis	Negative
			7/27/45	Hysterectomy	Epidermoid Ca Grade III	
TC 1294	9/4/45 positive	0	8/31/45	Biopsy	Chronic cervicitis	Suspicious
			9/ 7/45	Hysterectomy	Cancer in situ	
TC 311	11/17/45 positive	I	8/ 7/45	Biopsy	Chronic cervicitis	Suspicious
			9/21/46	Hysterectomy	Epidermoid Ca	
M 1054	1/23/46 positive	0	1/30/46	Biopsy	Inadequate	Negative
			2/13/46	Cervicectomy	Cancer in situ	
TC 1636	2/12/46 positive	II	2/12/46	Biopsy	Chronic cervicitis, sev.	Epidermoid Ca
			2/15/46	Hysterectomy	Epidermoid Ca	
M 1093	2/13/46 positive	0	2/13/46	Biopsy	Chronic cervicitis	Negative
			3/ 6/46	Hysterectomy	Cancer in situ	
TC 1766	3/30/46 suspicious	II	3/30/46	Biopsy	Acanthosis	Suspicious
	4/5/46 positive		4/ 6/46	Biopsy	Epidermoid Ca Grade III	
TC 2032	7/20/46 positive	IV	7/20/46	Biopsy	Probable Ca	Necrosis—no cellular details
			7/27/46	Biopsy	Necrosis	
TC 2219	10/19/46 positive	I	10/19/46	Biopsy	Chronic cervicitis with squamous metaplasia	Negative
			11/2/46	Biopsy	Epidermoid Ca Grade I	
TC 2331	11/27/46 positive	0	12/10/46	Biopsy	Chronic cervicitis	Negative
			2/ 4/47	Hysterectomy	Cancer in situ	
TC 2381	12/10/46 positive	0	12/14/46	Biopsy	Leukoplakia	Negative
			3/14/47	Hysterectomy	Cancer in situ	

*Includes the three cases in which the first vaginal smear was also negative for cancer.

clinical stage of the lesions in the nineteen cases missed on initial biopsy examination with the seventeen cases missed on the initial vaginal smear.

In this table it is seen that most of the cases missed by the first smear are relatively evenly spread among Stages I, II, and III, and only eight of the seventeen were Stage 0 or I. However, a majority of the cases missed by the first biopsy, fifteen out of nineteen, were early and possibly curable cases. In the preinvasive group alone this comparison is striking. There were a total of sixteen cases of cancer in situ in the 181 cases under study. The first biopsy failed to make a positive diagnosis in eight of these (Table II, Stage 0), but the first smear was positive for cancer in fourteen of the same sixteen cases.

Tables III and IV present details of the cases in which the diagnosis was missed by the first biopsy and first vaginal smear, respectively.

Summary

A comparison of the diagnostic accuracy of the vaginal smear and the standard biopsy technique has been made in 181 cases of epidermoid carcinoma of the cervix. The first biopsy report was correctly positive in 90 per cent of the series. The first vaginal smear report was positive in 91 per cent of the same cases. By a combination of the two methods, the correct diagnosis was initially obtained in 178 cases, or approximately 99 per cent of the group. The vaginal smear was more accurate than the biopsy in diagnosing the early carcinomas of the cervix in this series of cases.

From this study of cervical cancer we conclude: first, that the vaginal smear is diagnostically as reliable as the biopsy taken in a large general hospital; second, that an extremely high percentage of cases can be diagnosed accurately if the two methods are used together; and finally, that the vaginal smear is of especial value in the diagnosis of the very early malignant lesions of the cervix.

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PREGNANCY FOLLOWING TUBAL STERILIZATION

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PREGNANCY has occurred after hysterectomy and after bilateral salpingo-oöphorectomy. The only certain method of preventing conception is the complete removal of ovaries, tubes, and uterus. This operation is castration, but to the laity it is synonymous with sterilization. The latter term may also mean castration, but to the physician it signifies some procedure designed to prevent conception without interfering with ovarian function. The simplest method for preventing conception is to block the lumen of the Fallopian tubes. However the large number of operations on the tubes designed to prevent pregnancy indicate that the number of failures is large.

Eastman, in 1936, reviewed the various methods of sterilization in women. We are interested primarily in reporting our failures and the reasons for them, and not in a discussion of which is the best method.

Pregnancy after tubal ligation is unwelcome in most instances to the patient and her husband and is most disconcerting to the physician. The patient is subjected again to the risks of pregnancy and usually subjected a second time to the risk of a laparotomy.

In this report we are including all the cases in which various methods of sterilization were used, and the number of failures with each. We were impressed by the number of operations designated in various reports as the Madlener method, but which actually bore little resemblance in most instances to the original procedure designed by Madlener. We, too, thought that we had been using the Madlener, but to our surprise found that it was not according to the directions of the author. In the majority of the cases under consideration, the tube was clamped close to the uterus, using until 1944 a heavy Kocher clamp and then ligating with a silk suture below and above the crushed area of the tube. From 1944 to 1946, we used a Payr clamp, but persisted in crushing and ligating the tube close to the uterus. Since early 1946 we have been following the original Madlener technique as depicted in Fig. 1, crushing the tube in the proximal end of the outer third, and placing one silk or cotton suture in the area of the crush as well as tying through the crushed area. Madlener did not state the length of time he left the angiotribe in place preliminary to ligation, but we have been compressing the tube for one minute. The angiotribe described by Madlener was 7 mm. in width. Our Payr clamp is 8 mm. in width at the base, tapering to 3 mm. We use the widest part. None of the patients ligated since 1946 have to date returned pregnant.

Koller states that in three patients in whom the tubes were ligated near the fimbriated end a hydrosalpinx developed. We have not noted any enlarge-

ment of either tube in those patients who became pregnant after ligation and were again subjected to operation. Perhaps there are some changes in the tube adjacent to the uterus if the ligation is in the outer third, but, if so, these changes should increase the safety of the tubal ligation. The senior author has, in a number of cases, crushed and ligated the tube near the fimbriated end and then injected either 95 per cent alcohol or sodium morrhuate into the wall of the tube adjacent to the uterus. He has not used this routinely, but it certainly increases the safety of the operation.

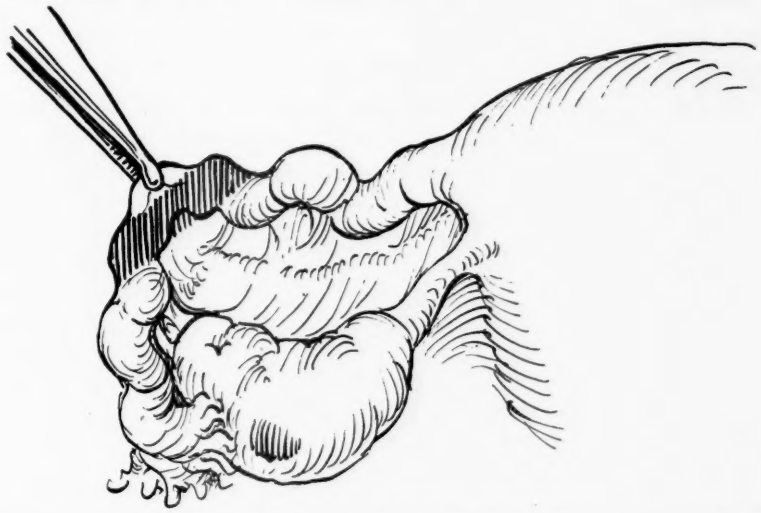

Fig. 1.—Loop in outer one-third of tube is crushed with Payr clamp for one minute and then ligated with silk or cotton suture. Care must be taken not to tie too tightly.

We have maintained that the simplest and most nontraumatic attack on the Fallopian tube is the procedure of choice; particularly is it justified if the results of this procedure are comparable to those of more extensive operative procedures. We are presenting cases of failed tubal ligations, performed either as a twenty-four-hour postpartum procedure or in conjunction with other operative obstetric or gynecologic procedures. We have made no attempt to follow every patient who submited herself for a tubal ligation, but have collected our data from the records of patients who have returned to us with a pregnancy following a ligation. We believe that we have, in this way, overlooked few failures for the well-recognized experience that these patients in whom ligations have failed are analogous to the vindictive customer who "wants her money back," and returns to demand it or to be reassured that she can't possibly be pregnant.

Unfortunately, we were unable to examine the site of ligation directly to ascertain the cause of failure in all of our cases, but in those who returned for a subsequent laparotomy the failures could be ascribed to either mistaken identity (one case) where the round ligament was ligated or to cases where the tubes were ligated but the lumen re-established, presumably as a result of an excessive constriction of the ligature which had either sheared or completely severed the tube.

It is not pertinent to our report, but since we have performed a large number of ligations, we are listing our indications for tubal ligation. The following complications or diseases may necessitate the termination of the reproductive career:

Obstetric: (1) Vascular-renal disease, (2) repeat cesarean section, and (3) repetition of major fetal abnormalities such as erythroblastosis.

Medical: (1) Heart disease, (2) diabetes mellitus or insipidus, (3) pulmonary tuberculosis, active or healed, but with extensive pathology, (4) neurologic and psychiatric disease, and (5) certain blood dyscrasias. Multiparity in association with minor medical or obstetric complications may justify tubal ligation. (The couple should have at least three healthy children.) (1) Epilepsy, particularly if there is a history of epilepsy in the family, (2) incapacitating varicosities of the vulva or lower extremities. (3) otosclerosis, (4) mental deficiency in either partner, (5) anxiety states resulting from the fear of future pregnancies, and (6) failure or the inability to use the usual methods of birth control.

We recognize the hazards of entering into the sociologic aspects of the problem of sterilization, particularly in regard to the justification of the procedure used with multiparity as the sole indication. However emphatically we may believe in the limitation of the family to that number of children which can be adequately cared for in that particular income level, *we have always insisted that there be some medical or obstetric indication for the interruption of future childbearing.*

TABLE I

	TOTAL NUMBER OBSTETRIC PATIENTS	PATIENTS STERILIZED (PER CENT)	STERILIZED AT CESAREAN SECTION (PER CENT)
C. Lull—Philadelphia Lying-In, 1924-1933	14,039	1.3	49
R. Knight—Sloane Hospital, 1934-1944	16,266	1.4	43
F. Irving—Boston Lying-in, 1934-1944	45,216		24
Chicago Lying-in, Jan. 1935–July 1945	31,930*	3.6†	48

*Including: vaginal deliveries, cesarean sections, patients with hysterectomy for purpose of therapeutic abortions, Porros.

†Including hysterectomies for purpose of therapeutic abortion and sterilization, and Porro or cesarean hysterectomies.

The data in Table I illustrate the incidence of tubal ligation on our service in the period under consideration. The explanation for the variance in our statistics from those of other services is undoubtedly to be found in the large group of multiparas, women with four or more children who present concomitantly a justifiable medical or obstetric indication for interruption of future childbearing. We suggest tubal ligation at the time of the second cesarean section and become insistent at the third cesarean section; however, *our policy now does not include the performance of cesarean section for the primary purpose of sterilization.*

Our statistics as presented in Table II are unfavorable. However, it must be remembered that our service is primarily a teaching one, and that though our staff patients are directly supervised by the senior staff departmental member,

TABLE II. MADLENER STERILIZATIONS

	NUMBER	FAILURES CASES	PER CENT
Von Graff (Collective review to 1938)	4,279	19	0.44
Adair and Brown	50	0	0
Dippel	101	5	4.9
Hewitt and Whitley	100	0	0
Pfeutze	165	3	1.9
Dieckmann-Hauser	912*	33†	3.6

*Majority were Madlener.
†All Madlener; one tubal resect.

TABLE III

FROM JANUARY 1, 1935 TO JULY 1, 1935	NUMBER OF CASES	NUMBER OF FAILURES	PERCENTAGE OF FAILURES
Cesarean section and tubal ligation	418	14	3.3
Twenty-four-hour tubal ligation	286	16	5.6
Abdominal tubal ligation (Gynecologic)	93	0	0
Hysterotomy and tubal ligation	77	1	1.3
Vaginal tubal ligation	38	2	5.2
Total	912	33	3.6%

the tubal ligations are usually done by the senior obstetric resident. The higher incidence of failures in the staff as compared to the private patients supports our belief that the competent surgeon need have a negligible incidence of failures. One of our senior staff members over a period of two odd decades has had no known failures in a sizeable series of his private patients.

When we analyze the failures of sterilization combined with another operative procedure or as a twenty-four-hour postpartum procedure we find as in Table III that one of our highest numbers of failures is found in the group of vaginal surgery, usually a vaginal plastic in combination with a tubal ligation from below. This is not surprising, as the difficulties encountered in adequate exposure are obvious in this manner of approach to the Fallopian tubes. Nor were we particularly surprised by the rather high incidence of failures in the twenty-four-hour postpartum group, for this is the group which is handled primarily by the senior resident, as are the ligations incident to the cesarean section group, where the senior staff member usually drops out, permitting the resident to perform the ligation and closure. It is of interest to note the lack of failures of ligations in combination with a laparotomy for gynecologic indications. One wonders whether the tube, altered by the normal pregnancy tissue changes, is less amenable to permanent closure or is so edematous and friable that the utmost of delicacy in the manipulation and ligating is necessary to prevent a cutting or shearing of the ligature and subsequent fistula formation.

We doubt that morbidity plays a significant role as a cause of failure inasmuch as the morbidity in the series of failed ligation incident to cesarean section or as a postpartum procedure did not differ appreciably from our overall morbidity for cesarean sections and vaginal deliveries.

Of less pertinence, but of some interest, are other minor data recovered in an analysis of our series. The minimum period between tubal ligation and subsequent pregnancy has been two months, the maximum thirty-nine months, and the average fourteen months. The fertility of this group of patients ranged from a minimum of two pregnancies to a maximum of nine, the average 4.1. Lactation did not appear to be of significance: sixteen patients did not nurse, six did, and on eight patients no relevant information was obtainable. The youngest patient at the time of the tubal ligation in whom a failure occurred was 20 years, the oldest 43 years, and the average age was 28.3 years.

If the operative technique of tubal ligation has been carefully explained to the patient and her husband, there will be no psychic changes and no loss of libido. The menopause will not develop at an earlier age if the venous return from the ovary and tube is not obstructed.

Summary

We believe that the Madlener method of tubal crushing and ligation will prevent future pregnancies if it is properly carried out. It is the simplest and safest surgical procedure and can be performed at the time of a gynecologic operation, at the time of cesarean section, at the time of interruption of pregnancy by the abdominal route or as the twenty-four-hour procedure as advocated by our clinic.

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PENICILLIN VAGINAL SUPPOSITORIES AND THE PREVENTION OF POSTPARTUM MORBIDITY

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PUERPERAL infection has been one of the leading causes of maternal death for many years. In recent years, death from infection has been greatly reduced since the introduction of the sulfonamides and antibiotic drugs. However, morbidity during delivery and the puerperium has not decreased in a like manner.

In a teaching institution such as the Cincinnati General Hospital, there are many individuals involved in the preparation, delivery, and aftercare of women entering the hospital for obstetric care. Contamination before, during, and after delivery undoubtedly accounts for a large proportion of morbidity in obstetric cases. Morbidity reports from various centers throughout the country range from approximately 3.3 per cent corrected to as high as 10.5 per cent corrected. Our own morbidity figures (Table I) range from a low of 5.7 per cent in 1941 to a high of 10.3 per cent in 1944. The average morbidity due to genital tract infection was 7.84 per cent from 1936 to 1945, inclusive.

TABLE I. MORBIDITY DUE TO GENITAL TRACT INFECTION

YEAR	TOTAL DELIVERIES	NUMBER OF CASES OF GENITAL TRACT INFECTION	PER CENT
1936	2,114	123	5.8
1937	2,252	183	8.1
1938	2,497	201	8.1
1939	2,484	171	6.9
1940	2,542	181	7.1
1941	2,630	151	5.7
1942	2,604	218	8.3
1943	2,282	206	9.0
1944	1,835	188	10.3
1945	1,885	171	9.1
1946			
1947, Jan. to June	1,434	80	6.7

Since infected cases require isolation, increased nursing care and increased time in the hospital and, believing that most of the infection was exogenous and occurred during labor and delivery, it was decided to use penicillin locally in the form of vaginal suppositories* containing 100,000 units of penicillin each. The alternate case method was chosen, and only cesarean section cases were excluded. The standard method for determining morbidity was used. The figures have been corrected, and include only cases of genital tract infection associated with episiotomy or laceration, endometritis, parametritis, and pelvic thrombophlebitis. There were no cases of thrombophlebitis of the lower extremities. Infinite care is taken by the staff of this service in making the diagnosis. Morbidity is based on a temperature elevation to 100.4° F. any two days following the first day of the puerperium.

*Penicillin Vaginal Suppositories furnished by Schenley Laboratories, Inc.

TABLE II. MORBIDITY DUE TO GENITAL TRACT INFECTION

YEAR	TOTAL DELIVERIES	NUMBER OF CASES OF GENITAL TRACT INFECTION	PER CENT
1946-1947			
July to Mar., 1947	1,573	60	3.8
Penicillin	778	18	2.3
No penicillin	795	42	5.3

There were 1,573 cases in the series (Table II); 778 received 200,000 units of penicillin in the form of cocoa butter suppositories inserted into the posterior fornix of the vagina with a sponge forceps immediately following delivery. There were 795 cases used as controls who received no penicillin. From January to June, inclusive, 1946, there were 1,434 deliveries. There were 80 cases of genital tract infection, or a morbidity rate of 6.7 per cent. The series of 1,573 was begun in July, 1946, and continued through the middle of March, 1947. There were 60 cases of genital tract infection, or 3.8 per cent morbidity for this group. Of the 778 patients receiving penicillin vaginal suppositories, 18, or 2.3 per cent, developed genital tract infection. Forty-two of the 60 patients developing morbidity were in the untreated group of 795 cases. Thus the morbidity rate for this latter group was 5.3 per cent.

Of the 18 patients developing genital tract infection who received penicillin, 14, or 77.7 per cent, had either episiotomy or lacerations repaired. Of the 42 patients who developed infection who did not receive penicillin, 20 cases, or 47.8 per cent, had either laceration or episiotomy. In the entire group 428 cases, or 55 per cent, of those patients receiving penicillin post partum had either episiotomy or lacerations. In the control groups, 357 patients or 44.9 per cent, had either episiotomy or laceration. Thirty-four, or 56.6 per cent, of the patients developing morbidity had either episiotomy or laceration.

Statistical study of the effect of these complications is not warranted when the control or alternate case method is considered. The difference between the treated (2.3 per cent) and the untreated (5.3 per cent) is statistically significant.

Penicillin blood levels were tested on 49 patients. The Randall, Welch, and Price method was used with *B. subtilis*, the test organism. Eleven cases failed to develop blood levels. Thirty-eight cases had blood levels averaging 0.06 units per c.c. of serum in one-half hour, 0.06 to 0.25 units at one hour, and 0.06 to 1.00 at two hours. All but five cases who had levels, maintained them for at least two hours. The two-hour levels on these five showed no penicillin. The absorption seemed to depend somewhat on the amount of bleeding post partum plus the vigorous massage of the fundus which some patients inevitably receive.

It is regrettable that funds were not available for adequate blood levels to learn if local or general effects were obtained and to establish the dosage.

Summary

1. Seven hundred and seventy-eight of 1,573 cases in the group received 200,000 units of penicillin per vaginam immediately after delivery with a morbidity rate due to genital tract infection of only 2.3 per cent.

2. In the control group of 795 cases, the morbidity rate corrected was 5.3 per cent.

3. The morbidity rate of 3.8 per cent for the entire group of 1,573 cases was considerably less than the 6.7 per cent rate encountered in the first half of 1946, and the average of 7.84 per cent for the past ten years.

4. Blood levels were obtained with intravaginal penicillin in 77.5 per cent of cases on which levels were tested.

5. No local or systemic reactions were noted.

6. There was no definite relationship between development of morbidity and perineal wounds.

Conclusions

1. The use of penicillin in the form of vaginal suppositories at the time of delivery definitely reduced the puerperal morbidity rate on our service.

2. This preparation should be of particular value in cases which become morbid after early rupture of membranes, long labor, and where genital tract infection is suspected.

3. The use routinely of penicillin vaginal suppositories after delivery is justified because of the reduction of the nursing care required, in infected cases, reduction in number of extra hospital days required per patient, and particularly a reduction in genital tract infection following delivery.

I wish to express my appreciation for the valuable suggestions given to me by Dr. Marion A. Blankenhorn, Professor of Medicine, and Dr. Morton F. Hamburger in the preparation of this publication, and to Dr. Ralph Heery for his aid in the laboratory work.

MALIGNANT GRANULOSA-CELL TUMOR IN AN INTRASPLENIC OVARIAN GRAFT IN A CASTRATED MALE MOUSE*

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GRANULOSA-CELL tumors and luteomas have developed in intrasplenic ovarian grafts in castrated male and female mice.[1, 2] More recent experiments showed that ovarian tumors have also formed in intrapancreatic ovarian grafts in castrated mice.[3] It is assumed that the prolonged stimulation by augmented amounts of gonadotrophic hormones of the hypophysis, to which the ovaries are subjected in this site, is responsible for the development of the neoplastic growths. In our previous studies, mitotic activity of the granulosa tumor cells and indications of invasion into the splenic tissues were observed in the tumors, although metastases were not noted and the tumors were not transplanted to determine the capacity for progressive growth in a new host. This paper is a report of metastasis and successful transplantation of a granulosa cell tumor.

Male and female mice of the A, C_3H, and C_{57} strains, and several groups of hybrid mice (A X C_3H and CBA X C_{57}) were used. They were castrated, and received, at the same time, an autoplastic or homoplastic ovarian graft in the spleen. Some of them were given subcutaneously weekly injections of 16 micrograms alpha-estradiol benzoate, 1.25 mg. testosterone propionate, or 1 mg. progesterone. Unilaterally gonadectomized mice with intrasplenic grafts served as controls. The experiments extended for a period of ten months.

Observations

Ovarian tumors appeared in intrasplenic ovarian grafts in mice of the A, C_3H, and C_{57} strains, and in hybrid mice. There is apparently no strain limitation in the development of tumors in autotransplants or homotransplants of ovaries in castrated mice. Ovarian tumors have not been observed in intrasplenic ovarian grafts in unilaterally gonadectomized male and female mice. The formation of tumors in intrasplenic ovarian grafts did not occur in mice receiving weekly administration of estradiol benzoate or testosterone propionate beginning fourteen to nineteen weeks after the ovaries were transplanted. Treatment with progesterone, however, was not effective under similar conditions.

Among 17 castrated male and female mice treated with progesterone, eight granulosa cell tumors, one luteoma, and three mixed cell tumors (granulosa and luteoma cells) were found in intrasplenic ovarian grafts from 213 to 284 days old. One nontumorous graft was one hundred and ninety-three days old. No tumor was noted in four grafts with vascularized adhesions that permitted drainage through other than the hepatic portal system. Metastasis of one granulosa-cell tumor into the liver was observed in a castrated male mouse of

*Presented at the Annual Meeting of the American Association for Cancer Research, May 16, 1947, at Chicago, and the New England Cancer Society, May 23, 1947, at New Haven, Conn. This research has been aided by grants from The Anna Fuller Fund and The Jane Coffin Childs Memorial Fund for Medical Research.

†The Anna Fuller Fund Fellow in Anatomy.

the A strain bearing an intrasplenic graft for two hundred and thirteen days. This animal had received nine weekly subcutaneous injections of 1 mg. progesterone dissolved in sesame oil starting one hundred and thirty-eight days after the grafting. The tumorous graft was reddish yellow, solid and measured 14.5 by 15 by 21 mm. in diameter. The tumor received a collateral vascular supply from the pancreas. The spleen was normal in size, but most of the distal portion merged into the tumor. The liver was brownish red in color, and several

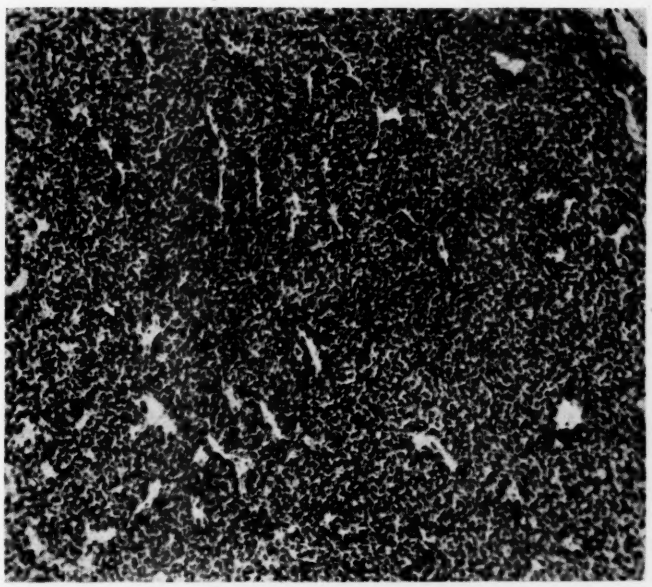

Fig. 1.—Section of a granulosa cell tumor in an intrasplenic ovarian graft (213 days) in a castrated male mouse. (×85.)

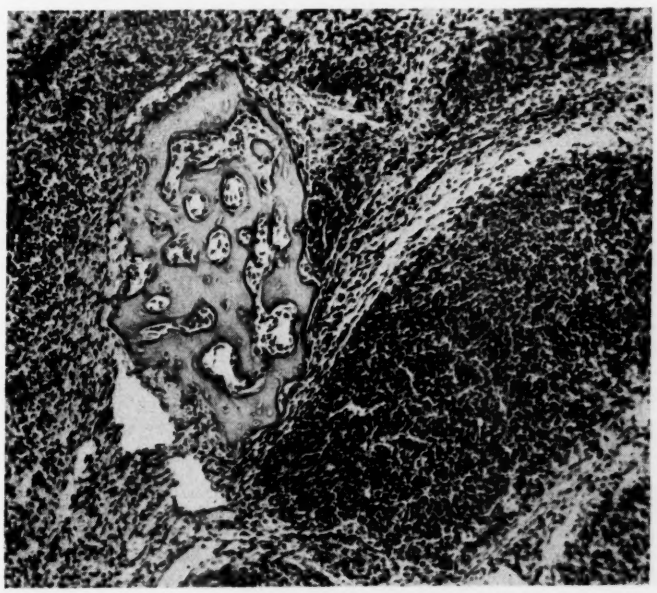

Fig. 2.—Section showing a spicule of bone at the junction between the tumor and splenic tissue (left side). (×85.)

small metastatic foci were observed. Abdominal ascites and pleural effusion were present. The small urinary bladder was distended with urine, and the seminal vesicles and prostates were atrophic. Other visceral organs and pituitary gland appeared normal.

Microscopic examination revealed that the tumor was incompletely encapsulated and composed of compact masses of granulosa tumor cells showing numerous mitotic figures (Fig. 1). Some masses of tumor cells, however, were arranged in a folliculoid pattern. The germinal epithelium of the tumorous graft showed no extensive ingrowth. Luteinized cells and small necrotic areas were observed at the periphery. A spicule of bone was found at the junction between tumor and splenic tissue (Fig. 2), but in an area showing no necrosis. The metastatic granulosa tumor cells in the liver were aggregated in nodular masses situated adjacent to hepatic sinusoids or veins (Fig. 3). Each large, solitary granulosa-cell mass exhibited histologically a miniature of the primary tumor in the spleen (Fig. 4). The nuclei of tumor cells were hyperchromatic, and mitoses were common.

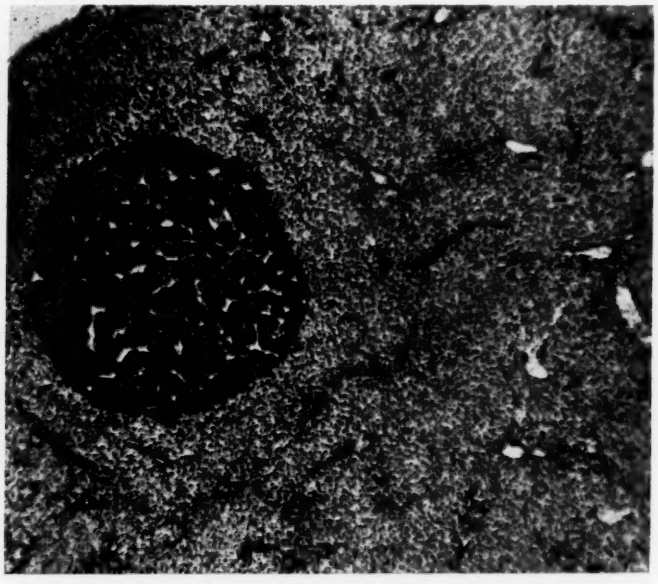

Fig. 3.—A metastatic nodule of the granulosa cell tumor in the liver. (×30, approx.)

The granulosa cell tumor was transplanted by inserting small fragments subcutaneously along the right lateral body wall through a thirteen-gauge hypodermic needle fitted with a plunger. Ten mice (six castrated males, two castrated females, and two intact males) of the A strain, one castrated female mouse of the C_3H strain, and two castrated female mice of the CBA strain were used as hosts. All of them received four weekly injections of 1 mg. progesterone subsequent to the transplantation. Progressive growth of transplanted tumors was noted in one castrated female mouse of the A strain, and in two castrated male mice of the same strain.

The castrated female host was killed seventy-three days after the transplantation. Constant estrous vaginal smears were noted during the last thirty days; and the uterus weighed 120 mg. at autopsy. The transplanted tumor was very well vascularized, and measured 12 by 20 by 22 mm. in diameter. Histologically, the transplanted tumor resembled the original tumor (Fig. 5), except that some of the folliculoid masses contained hemorrhagic cavities.

The transplanted granulosa cell tumor from the castrated female host was further inoculated subcutaneously into ten castrated male and female mice of the A strain, but progesterone was not injected. The transplants in the second passage are growing rapidly in all of the hosts.

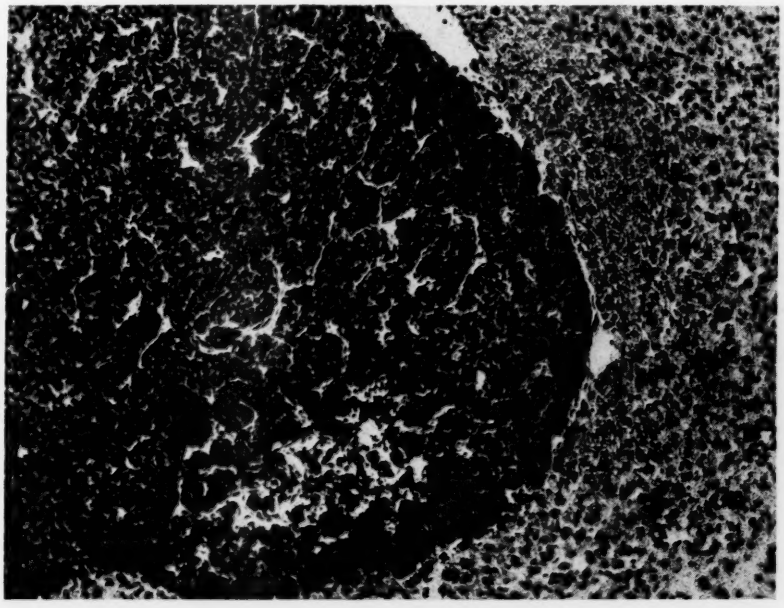

Fig. 4.—Higher magnification of metastatic granulosa tumor cells in the liver. (×180.)

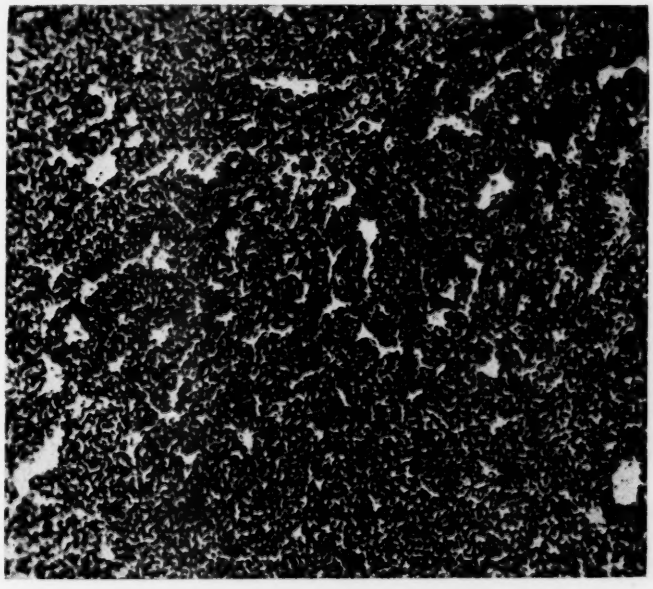

Fig. 5.—Section of a subcutaneously transplanted granulosa cell tumor (73 days) in a castrated female mouse. (×90.)

Discussion

The administration of progesterone in weekly doses of 1 mg. did not inhibit tumor formation in intrasplenic ovarian grafts in castrated mice. On the other hand, the doses of estradiol benzoate and testosterone propionate, and endogenous hormones from one intact gonad exerted an inhibitory influence.

The first granulosa-cell tumor successfully transplanted in a mouse arose spontaneously in an untreated animal, and the transplanted tumors secreted estrogen.[4] The ability of metastasis and transplantability in new hosts indicated the malignancy of granulosa-cell tumors developed in intrasplenic ovarian grafts. In this respect the tumors resembled ovarian tumors developed in the ovaries of x-rayed mice.[5]

Summary

A transplantable granulosa cell tumor with metastasis in the liver developed in an intrasplenic ovarian graft in a castrated male mouse. The present experimental result indicated that granulosa cell tumors induced in intrasplenic ovarian grafts may become malignant growths.

Grateful acknowledgment is made to Dr. E. Schwenk of the Schering Corporation for the alpha-estradiol benzoate (Progynon-B), testosterone propionate (Oreton), and progesterone (Proluton); and to Dr. E. Oppenheimer of the Ciba Pharmaceutical Products, Inc., for the progesterone.

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A NINE-YEAR FOLLOW-UP IN CASES OF TOXEMIA OF PREGNANCY*

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THE toxemia clinic was established at the Long Island College Hospital in September, 1937. To this clinic are referred all prenatal patients showing evidence of a developing toxemia of pregnancy. Also referred to this clinic are all patients with a history of a toxemia in a previous pregnancy whether it occurred in our institution or elsewhere, as well as those patients who have a history or evidence of vascular-renal disease. All patients are encouraged to return to this clinic at periodic intervals after delivery in the hope that we may be able to evaluate the effects of the toxemias upon these patients in later life as well as in subsequent pregnancies.

This study is based on a review of the records of 391 women of a total of 530 toxemia clinic patients who were carried through 968 pregnancies. Six hundred eighty-five of these pregnancies were associated with toxemia or vascular-renal disease. The remaining 283 pregnancies were normal following a previous toxemia.

Of the 391 patients who exhibited true toxemia of pregnancy, thirteen had eclampsia, 275 were classified as pre-eclampsia mild, and 103 as pre-eclampsia severe. This report is limited to an analysis of the late results in this particular group of patients, and is concerned chiefly with the incidence of residual damage. The most common evidence of residual damage is an elevated blood pressure. In only a few cases, with the tests at present available, has there been shown to be any definite renal impairment. Three hundred three patients in this group were seen on one or more occasions after discharge from the hospital, the period after delivery varying from a few weeks to a number of years, the longest follow-up period being nineteen years in one patient. In the remaining cases, the diagnosis of residual damage or its absence is of necessity based upon the blood pressure course and blood and urine studies made in the hospital in the immediate puerperium.

Eclampsia

The records of only thirteen cases of eclampsia have been encountered in this study, too small a group to warrant the drawing of any conclusions. However, it is of interest that four of these (30.7 per cent) showed evidence of residual damage. All but one of them occurred in the first pregnancy. All were under 25 years of age. The presence of residual damage was based on follow-up study of three months in two, three years in one, and five years in the fourth. The shortest follow-up period in those without residual damage was three years, the longest seventeen years, and all were followed through subsequent pregnancies.

Two other patients gave a history of having had eclampsia previously, were followed through another pregnancy in our clinic, and showed no evidence of residual damage at four and seven years, respectively.

*Read, by invitation, before the New York Obstetrical Society, March 11, 1947.

Pre-eclampsia

Three hundred seventy-eight patients had pre-eclampsia in at least one pregnancy. Sixty of these women had pre-eclampsia with more than one pregnancy. The pre-eclamptic toxemias were listed as mild or severe according to the criteria advanced by the American Committee on Maternal Health. Of the 275 cases classified in the mild group, seventy (25.4 per cent) had hypertension subsequent to the toxemia. Among the 103 severe cases, residual damage occurred in forty-four (42.7 per cent). When these two groups are combined, making a total of 378 patients with pre-eclampsia, the incidence of residual damage is found to be 30.1 per cent (114 cases).

The time that elapses from the onset of the first signs and symptoms of a toxemia to termination of the pregnancy, in other words duration of toxemia, has been emphasized repeatedly as a dominant factor in the incidence of residual damage.[1-7] The statement has been made that toxemia should not be allowed to persist for more than three weeks because of the increased danger of late damage.[8-10]

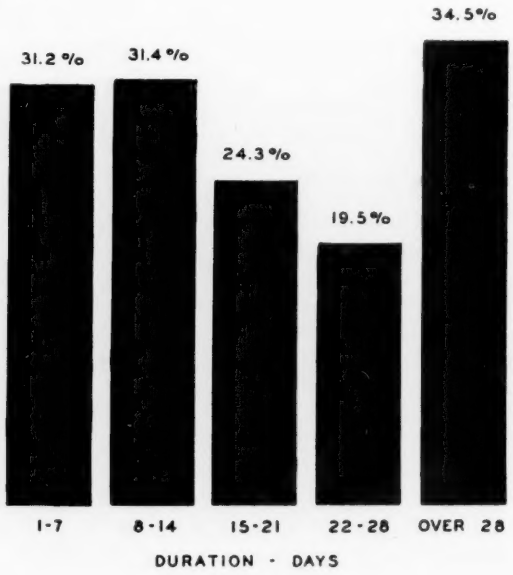

Fig. 1.

Hence we have grouped all of our patients with pre-eclampsia according to duration of the toxemias as follows: one to seven, eight to fourteen, fifteen to twenty-one, twenty-two to twenty-eight, and over twenty-eight days. The result of this grouping is shown clearly in Fig. 1. It is seen that *residual damage does not increase progressively with increased duration of the toxemia.* When the toxemia was allowed to run for one to seven days, late damage occurred in 31.2 per cent of 128 cases; eight to fourteen days in 31.4 per cent of 54 cases; fifteen to twenty-one days in 24.3 per cent of 37 cases; twenty-two to twenty-eight days in 19.5 per cent of 46 cases, and over twenty-eight days in 34.5 per cent of 113 cases. The incidence of late damage is highest in that group in which the toxemia persisted for longer than four weeks. Yet it is only slightly higher than it is in the one-week or the two-week groups, whereas it is considerably higher than it is in the three- and four-week groups.

The cases were also grouped according to age at the time of the pre-eclamptic pregnancy. If a patient had toxemia with more than one pregnancy,

as sixty did, she was listed according to her age with her first toxemia. Fig. 2 shows the results of this grouping. There is seen to be a *definite relationship between age at the time of the toxemia and the incidence of residual damage. Late damage increases progressively with age.* At the age of fifteen to twenty years 13.1 per cent of 61 cases showed late damage; at twenty-one to twenty-five years, 21.1 per cent of 118 cases showed such damage; at 26 to 30 years, damage occurred in 28.5 per cent of 91 cases; at 31 to 35 years, in 48.9 per cent of 47 cases and over the age of 35 years, 52.4 per cent of 61 patients showed evidence of residual damage. Table I gives the number of patients in each age and in each duration group.

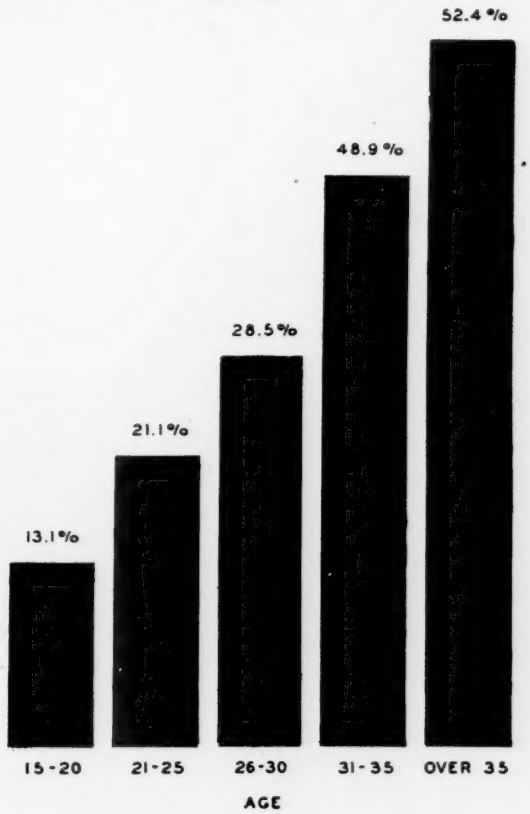

Fig. 2.

Fig. 3 shows again the incidence of residual damage in each age group. It also shows the percentage of patients in each group in which duration of the toxemia was less than three weeks and over three weeks. As may be observed, the percentage of patients in whom the toxemia lasted three weeks or longer is almost the same for each age group. It would seem, therefore, that *age, rather than the duration of the toxemia, is the determining factor.*

The finding of hypertension in a patient who has had pre-eclampsia several months or years before often leads to the conclusion that this is evidence of residual damage. How many of these women would have had hypertension at a given time in life, even though they had never been pregnant? The importance of this question was emphasized by a group of thirty-three patients with hypertension complicating pregnancy. All of these thirty-three women had been pregnant before, and all of their previous pregnancies were known to have been normal. At the time of the hyper-

tensive pregnancy, four of these patients were between 20 and 25 years of age, five between 26 and 30 years, ten between 31 and 35 years, and thirteen over 35 years. In one, the age was not stated.

There was another group of patients, eleven in number, whose records showed pre-eclampsia followed by one or more perfectly normal pregnancies,

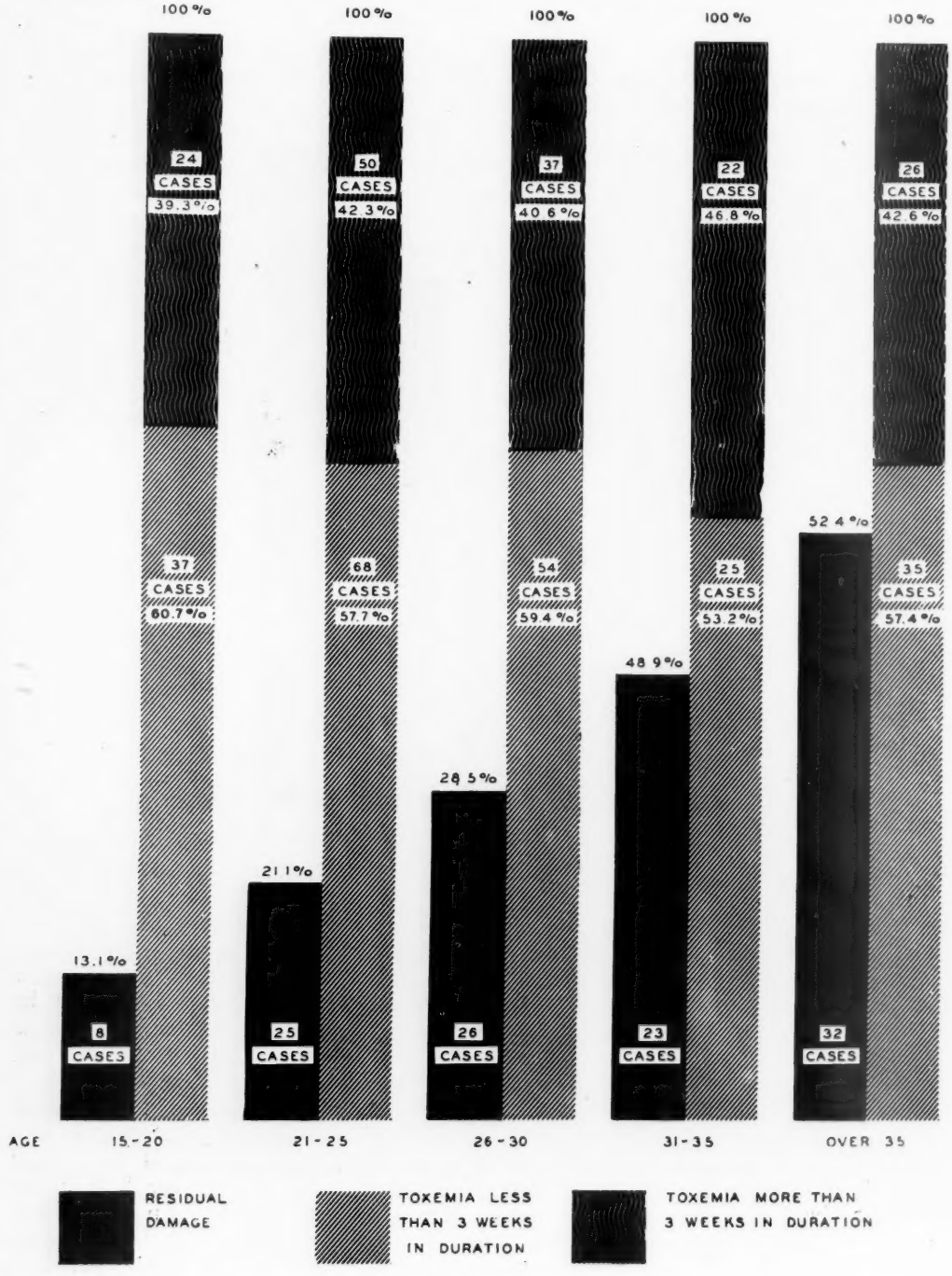

Fig. 3.

TABLE I

	NO RESIDUAL DAMAGE					WITH RESIDUAL DAMAGE				
AGE (DAYS)	1-7	8-14	15-21	22-28	OVER 28	1-7	8-14	15-21	22-28	OVER 28
15-20	16	9	5	5	18	4	1	2	0	1
21-25	36	8	12	11	26	8	4	0	1	12
26-30	20	6	9	15	15	12	6	1	3	4
31-35	6	5	2	4	7	7	3	2	0	11
Over 35	10	9	0	2	8	9	3	4	5	11

which were in turn followed by a pregnancy associated with hypertension. These eleven patients may be listed, as they were in this study, as showing residual damage, latent perhaps, due to the previous pre-eclampsia. On the other hand, it might well be that these eleven patients would have had hypertension at this particular time in life had all of their previous pregnancies been normal, or even had they never been pregnant.

Summary

A study has been made of the records of 530 patients seen in the toxemia clinic of the Long Island College Hospital. These 530 patients had 968 pregnancies, of which 685 were associated with toxemia or vascular-renal disease, and 283 were normal.

Three hundred ninety-one patients showed evidence of true toxemia of pregnancy. These form the basis of this report.

This study indicates that duration of the toxemia has little bearing upon the incidence of residual damage.

It shows however, that age is a more important factor, the incidence of residual damage progressively increasing with the age of the patient.

The validity of the assumption that hypertension occurring after a toxemia is due to residual damage is questioned.

Evidence is given in support of the conclusion that such hypertension in some cases would have occurred had the patient never become pregnant.

I wish to thank Doctor Alfred C. Beck for the privilege of conducting the Toxemia Clinic and to acknowledge my gratitude to Doctor Mervyn V. Armstrong and the other members of the obstetrical and gynecological staff for their cooperation in the study and management of these toxemia patients.

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HEPARIN IN THE TREATMENT OF TOXEMIA OF PREGNANCY

A Preliminary Report

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THE pathologic changes which are found in women who die from toxemia of pregnancy are frequently neither consistent nor pathognomonic. However, numerous writers have observed certain changes which occur with quite some regularity. These, in general, consist of diffuse scattered capillary or arteriolar lesions in different organs.[1] The presence of thrombi in these vessels, and the frequency of isoagglutination reactions in pregnant patients, not infrequently observed, has impressed the authors of their probable importance in the pathogenesis of toxemia of pregnancy.

In 1902, Flexner[2] demonstrated the presence of agglutinated erythrocytes associated with thromboses in the smaller vessels of the liver, and observed that these were in the neighborhood of the areas of necrosis and hemorrhage. Dienst, in 1905,[3] suggested that fetal erythrocytes reached the maternal circulation, and there gave rise to agglutination. Boyd[4] states that symmetrical cortical necrosis, as seen occasionally in eclamptics, is caused by thrombosis of the interlobular arteries and afferent arterioles. Yamada[5] has suggested or hinted that toxemia of pregnancy is due to allergy and some special sensitization related to a toxin. That isoagglutination is much more common in pregnant women, and especially so in those with eclampsia, has been stated by Dexter and Weiss,[6] and noted by others.

The probability that the peripheral necrotic lesions at times observed in eclamptic patients are due to vascular thrombi is suggested by Dexter and Weiss.[7] They have considered the explanation to lie in the character of the hepatic circulation: The liver cells receive nourishment from the hepatic sinusoids whose blood is obtained from branches of both portal vein and hepatic artery. However, some of the interlobular branches of the hepatic artery supply directly the peripheral zone of the lobule with capillaries, and since the liver cells depend on their oxygen supply from the capillaries of the hepatic artery, thrombosis of these individual vessels lead to infarction.

M. Knisely[8] first observed agglutination of red blood cells in the conjunctival vessels of an eclamptic patient. Working along this same line of investigation, Odell, Aragon and Pottinger observed this phenomenon in several patients with eclampsia and have described this condition of intravascular clotting as "sludged" blood. They consider these findings of particular importance.[9]

Dieckmann[10] states in his monograph on the *Toxemias of Pregnancy* that the fibrinogen concentration in the blood averages 0.26 in nonpregnant individuals, whereas in pregnancy it is definitely increased to an average of 0.48 at term, with a range of 0.3 to 0.7 Gm. per cent. In eclampsia he has stated that the fibrinogen content of the blood occasionally exceeds 1 per cent in concentration. He and Schwarz have postulated that the lesion of eclampsia could be produced by substances entering the portal circulation from the intestine. They

suggest that these substances (including tissue fibrinogen or the like) could cause a decrease in the coagulation time of the blood in the portal system because the factors normally present to neutralize these substances are relatively decreased in the process of neutralizing chorionic tissue fibrinogen. Such decreased coagulation time would predispose to thrombosis in the portal vein or liver sinusoids.

Jorpes[11] refers to the fact in his monograph on heparin, that the substance inhibits to some degree isoagglutination of red blood cells and that it has some effect or action in immunization processes. He has also stated that the effect of heparin is not longer than three to six hours, when given by single intravenous injection; and that it can be immediately counteracted by intravenous protamine sulfate or by transfusion. It is known that when the drug is given by slow intravenous drip, the duration of its action is for only thirty to sixty minutes after the infusion is stopped. Barnes and Erwin[12] have demonstrated that blood loss in the puerperium is not increased by the administration of heparin or dicumarol. These facts led us to conclude that the administration of heparin in pregnancy complicated by toxemia should be an inocuous procedure if used with reasonable care.

One of us (H. Z.) had gained considerable experience in the use of heparin in the treatment of deep thrombosis of the lower extremities[13] and, in addition, had for some time considered its use in some of the systemic diseases involving thrombi in small vessels and capillaries. The anticoagulant action of this substance (heparin), as well as its reported (Jorpes[11]) and apparent (J. M.[14]) ability to inhibit agglutination, led us to believe that it might have an effect in preventing the progressive changes in toxemia of pregnancy. With this in mind, a pre-eclamptic patient was treated by one of us (J. M.) at Woman's Hospital. The case history follows:

J. B. (No. 92,903), a 33-year-old unmarried primigravida was first admitted Feb. 22, 1947, as an emergency because of vaginal bleeding of 36 hours, marked edema, headache, and drowsiness for several weeks. She had had no medical care for eight weeks and only irregularly prior to that. Early in her pregnancy she was told that "all was well," but eight weeks prior to admission, her doctor, in another city, told her "complications were developing."

Past history: The last menstrual period was believed to have been in August, 1946. The menstrual history was otherwise normal. A review of the medical and surgical history contributed no pertinent information. There was no apparent evidence of previous hepatorenal disease.

Physical examination found a short, stocky female, edematous, drowsy, and obviously sick. The skin was moist and clammy, and there was marked pitting edema of the hands, feet, and sacral area. The ocular fundi presented no apparent abnormalities, nor did the heart and lungs. The blood pressure was 184/90, pulse 100, and temperature 98.8° F. The gravid uterus was estimated to contain a pregnancy of twenty-five to twenty-eight weeks gestation. The fetal heart was strong in the left lower quadrant. Vaginal examination showed the cervix closed, moderately eroded, and thick, and the presenting part to be high and to the left. The remainder of the examination was essentially normal.

Laboratory investigation showed the urine concentrated. A catheterized specimen contained 4 albumin, "nearly solid," and an occasional leucocyte. The hemoglobin was 10.5 Gm. with 3.89 million red blood cells per cubic millimeter. The leucocyte count was 5,680 per cubic millimeter, and the differential smear was normal. Urea nitrogen, the morning after admission, was 15.5

mg. per cent, the uric acid 2.8 mg. per cent, and the carbon dioxide combining power 55.7 volumes per cent. The blood type was B, Rh positive, and the prothrombin time normal.

The patient was treated with 20.0 c.c. of 10 per cent magnesium sulfate, and 50.0 c.c. of 50 per cent dextrose intravenously repeated for two days, and, in addition, was given phenobarbital, morphia, colonic irrigations, high protein diet, etc. The response to this treatment was gradual improvement, manifested by progressive lowering of the blood pressure, which finally reached less than 140/80 on the sixth day (Fig. 1). During this time, the urinary albumin varied from day to day (0.2 to 0.8 Gm. per liter) and persisted until her discharge (Fig. 2). The subjective symptoms paralleled the laboratory findings; headache and edema continued until the seventh day. On the eighth day a sudden episode of vaginal bleeding was noted, though this subsided rapidly and she was discharged improved on March 7, 1947.

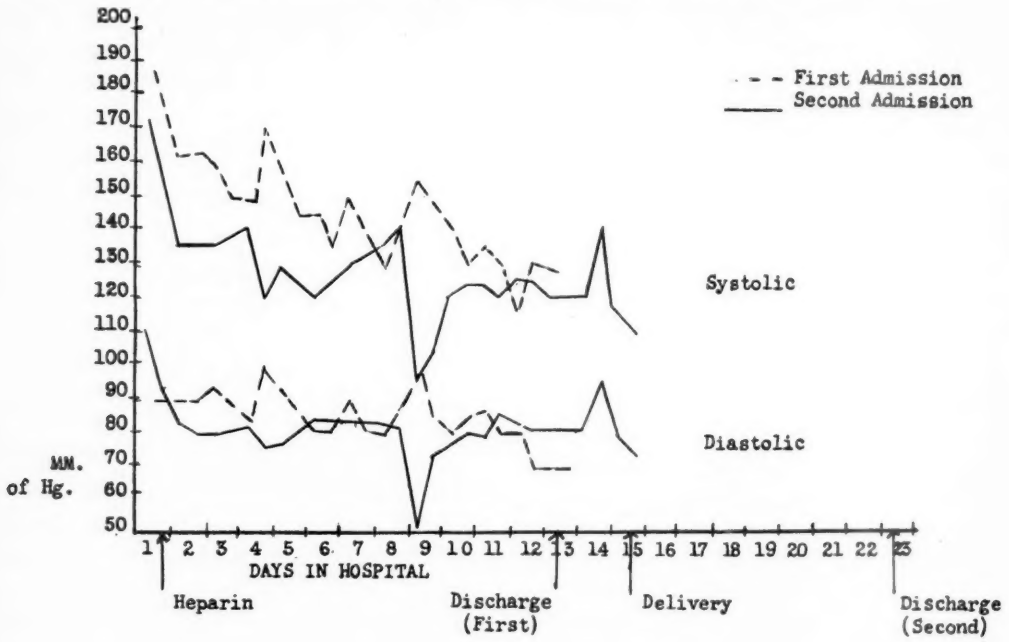

Fig. 1.

The patient was examined every two days in the outpatient clinic thereafter until March 31, during which time she developed progressive hypertension and an increased amount of urinary albumin. On this latter date, she was readmitted because of blurred vision, headache, some edema, and blood pressure of 170/110.

After six hours of bed rest, the blood pressure was 156/94. Physical examination showed slight edema of the feet, ankles, and upper extremities. The ocular fundi were unchanged, as was the remainder of the physical examination, except for the growth of the pregnancy. The catheterized urine at this time showed 1.6 Gm. per liter of albumin, and in addition masses of red blood cells and a few hyalin and granular casts which had not been present on the original admission. The urea nitrogen was 11.8 mg. per cent, and uric acid, 4.1 mg. per cent.

Since it had not been decided to use heparin in the treatment of toxemia when this patient was admitted, she again received intravenous glucose at 3, 6, and 9 P.M. on the day of admission, and again at 4:45 A.M. the following morning. In addition, magnesium sulfate was given at 6 P.M. and 4:45 A.M. the

evening of admission and the following morning, respectively. At 9 P.M. on the evening of admission, a continuous intravenous infusion containing heparin in distilled water and 5 per cent dextrose was started. This was discontinued at 1:30 A.M., April 1, 1947, because of impending labor, and after 150 mg. of heparin had been given. The clotting time which was normal prior to heparin was eighteen minutes by the Lee-White method when the drug was discontinued.

Following this treatment, the patient showed definite subjective and objective improvement. A catheterized urine the morning following admission showed only a trace of albumin which could not be measured. Subsequent analyses were similarly of small amounts, and in general remained substantially less than on the first admission. The drop in blood pressure is graphically shown (Fig. 1),

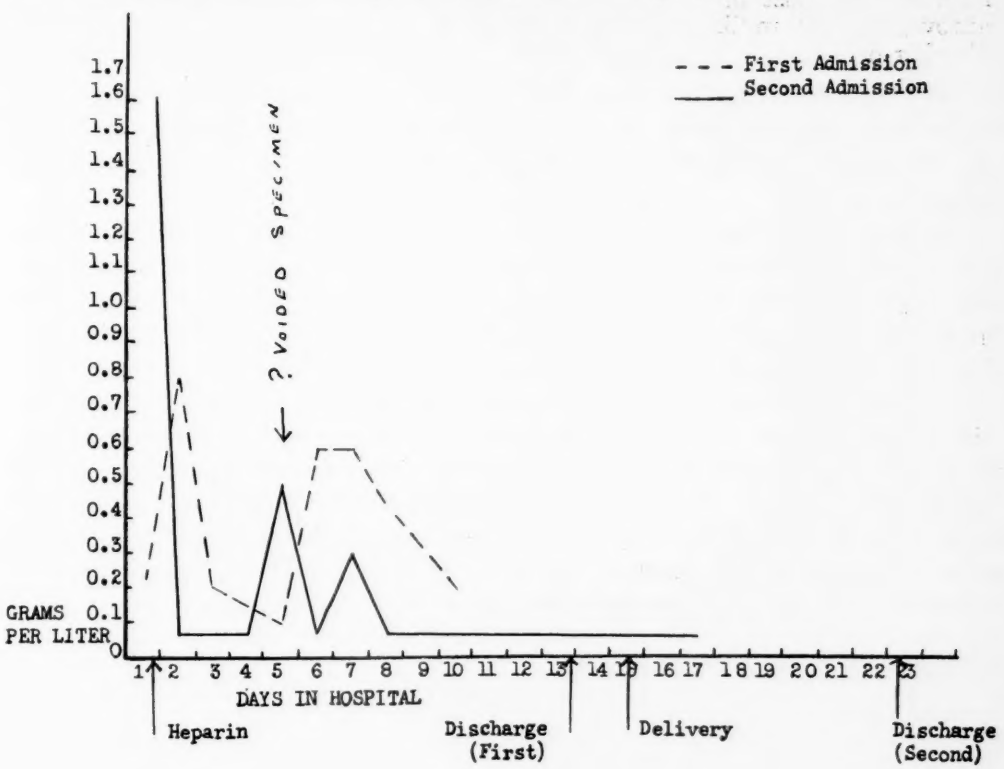

Fig. 2.

as is the urinary albumin (Fig. 2). It was noted that the blood pressure fell to less than 140/84 on the second day of hospitalization and, except for an occasional elevation, remained there or below. An episode of vertigo on the ninth day was associated with a dramatic, though temporary, drop in pressure. Progress continued satisfactorily except for some occasional unexplained nausea.

On the thirteenth day after an uneventful labor, she was delivered of a living infant weighing 1,616 Gm. Presentation was that of frank breech, and delivery was uncomplicated. The infant has made steady progress.

We have, in addition to the above case history, reports of three cases of toxemia of pregnancy treated in the University Obstetrical Clinic in Helsinki, Finland, under the direction of one of us (H. Z.). The records recently made available to us show that one of these, a 35-year-old primipara, was admitted with convulsions, a large amount of albumin in the urine, and a systolic blood pressure over 200. After four convulsions and death of the fetus, she was delivered per vagina by craniotomy and extraction. Following delivery the blood

pressure fell to 160/110 but then during six days steadily rose to 190/120. At this time she was given 400 mg. of heparin daily for two days with a resultant fall in blood pressure to 145/?. The drug was discontinued at this time and again the pressure rose to 180/110 in a period of about 24 hours. Upon readministration of heparin the tension in less than 48 hours fell to 130/90 or less and there remained until her discharge. The urinary output which was about 250 c.c. daily decreased to 90 c.c. on the sixth hospital day, when heparin was first administered. It then increased to 585 c.c. two days later and to 1,300 c.c. five days later. The intake during this time remained approximately 600 c.c.

The two other cases in which heparin was used show some evidence of beneficial effect, however, the results are equivocal because its use was limited to the first few days post partum. During this time both patients showed gradual improvement not unlike that which would be expected in any untreated case following delivery.

Discussion

The striking results obtained by the use of heparin in the above-described case and the results similarly obtained in Finland prompted this rather premature report.

It would seem that this case (J. B.) presented on the first admission laboratory and clinical evidence of pre-eclampsia. Its course under the usual therapy was gradual improvement, but albuminuria and hypertension rapidly recurred in the clinic. Similar findings, but with a much larger amount of albumin, were observed on the second admission.

It appears rather remarkable that following the use of heparin the urinary albumin fell from 1.6 Gm. to less than 0.1 Gm. per liter nine hours after treatment. In addition, there was diminution and gradual clearing of the cellular elements. Concomitantly, the blood pressure dropped to 140/84 or less and there remained except for two elevations on the eighth and tenth days. Even more important was the definite subjective improvement. Accurate intake and output records were not charted. In general, however, the urinary output was greater during the second admission than in the first few days of the first admission.

It is granted that bed rest alone will frequently lower blood pressure and albuminuria to some extent. However, toxemia is a progressive disease, and spontaneous cures are rare, provided the pregnancy is maintained. From the first admission the clinical course of the case presented is witness of this fact. Following heparin therapy, toxic signs and symptoms failed to return to any significant degree. It is believed that, had heparin been used repeatedly, even greater improvement would have been manifest. The results obtained in Finland certainly suggest that heparin had a very definite effect on the postpartum eclamptic status of one patient, as manifest by the concomitant drop in blood pressure and the rapid increase in urinary output after heparin was administered. The clinician who treated this one patient has informed us that prior to the use of heparin he was certain this patient would not survive.

Since these patients were observed, the work of Odell et al. has been brought to our attention, and we believe that their results further substantiate our rationale for treatment. The recently published investigations of Schneider[15] are of great interest. He has found that a toxic substance extracted from

placental tissue causes fatal multiple thrombi in mice when injected intravenously. The lesions in the liver of these experimental animals closely resemble the periportal necrosis of eclampsia. He concludes that this toxic substance is thromboplastin. It is known that the anticoagulant action of heparin is in part through its ability to neutralize thromboplastin.

Summary and Conclusions

1. Evidence from the literature has been presented to show that in pregnancy, and especially so in toxemia of pregnancy, at least one substance (fibrinogen) and possibly a second (thromboplastin) is present in increased amounts, and that in eclampsia the coagulation time of the blood is decreased, thereby predisposing to generalized diffuse thrombi.

2. It is believed that multiple, diffuse thrombi in small vessels associated with agglutination of red blood cells, particularly in parenchymatous organs, are instrumental in the clinical course of toxemia of pregnancy.

3. It is logical to assume that heparin, in part because of its anticoagulant action through its ability to neutralize thromboplastin and fibrinogen (?), and because of its antiagglutination effect, can inhibit the pathologic changes and favorably influence the clinical and laboratory findings.

4. A case of toxemia of pregnancy has been presented wherein two admissions, twenty-four days apart, were observed. During routine treatment on the first admission, gradual improvement was noted, but was followed by a return in force of symptoms after discharge. Abrupt and marked improvement which continued was observed nine hours after treatment with 150 mg. of intravenous heparin at a subsequent admission.

5. Three additional cases of toxemia treated in Finland have been mentioned. One of these, a severe toxemia with eclampsia continuing post partum, showed marked improvement after heparin therapy at a time when the prognosis was exceedingly grave.

6. Investigation is in progress to further establish the effect of heparin in this disease.

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PREGNANCY AND MULTIPLE SCLEROSIS

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MULTIPLE sclerosis as an entity has been studied quite exhaustively, and many articles about this condition have been published over the years. However, there appears to be a dearth of information about its course when complicated by pregnancy. A splendid review of the literature by C. H. Peckham appeared in the *New York State Journal of Medicine* **45**: 618, 1945. The author recounted the number of cases found in the literature of foreign countries and mentioned how little has been written in our own country on multiple sclerosis and pregnancy.

Little we can say about the etiology of multiple sclerosis, its signs and symptoms, etc., could add to that already known, but Peckham asks the question: "What effect, if any, does multiple sclerosis have on pregnancy, labor, and the puerperium?" Also, he makes a plea that reports of cases of multiple sclerosis complicated by pregnancy should be made in order to increase our knowledge of the relationship between the two conditions.

Since 1939, there have been seen at the University Hospital in Baltimore, Maryland, five cases of multiple sclerosis associated with pregnancy; one in 1939, two in 1943, and two in 1946. A brief résumé of the cases and their treatment follows:

Case Reports

CASE 1.—M. H. The patient, a 34-year-old white woman, was first observed in the hospital in January, 1937. Her chief complaint was difficulty in walking, with weakness of both ankles. She stated that the onset of the condition dated back to 1934 when she "sprained" her right ankle. Since then, the patient has been unable to flex the right foot and noted some foot drop. She had to "pick up" and "put down" her right foot. Physical examination revealed a complete paralysis of dorso flexion on both sides (feet and legs). Inversion and eversion of right foot impossible with the two factors greatly reduced on the left. Peroneal muscles of both sides atrophied as well as the intrinsic muscles of the feet. Laboratory work was as follows: red blood cells, 3,900,000; white blood cells, 5,420; hemoglobin, 88 per cent; serologic test for syphilis was negative. Spinal tap revealed clear fluid with pressure of 100 mm. of H_2O; Quakenstead—negative; Wassermann and mastic tests—negative; cell count—negative for white blood cells, showing a trace of globulin. Her family and past histories were noncontributory, and past obstetric history revealed one abortion (year not obtained). The patient was discharged after six days' hospitalization, and was followed routinely on the outside. She was readmitted to the hospital on Jan. 1, 1939, at term, having gone through a prenatal period which was essentially negative. The multiple sclerosis was not aggravated by her pregnancy, and the findings were essentially the same as when she was first seen. Following fourteen hours of not too severe labor, she delivered a full-term living child weighing 6 pounds 8 ounces. Her postpartum course was uneventful, with no exacerbation of her condition.

Patient has been seen several times since 1939 and her condition remains unchanged. There has been no noticeable advance of the disease except for some increase in generalized weakness. There have been no other pregnancies or abortions and when last seen in April, 1946, her condition was satisfactory.

CASE 2.—E. H. The patient, a 23-year-old colored para 1-0-0-1 was first seen in the accident room on November 8, 1940, because of disturbance of gait of some 18 months' duration. Her history dated back to March, 1939, when, while out walking, she suddenly fell to the ground. She attempted to get up but her legs were so weak that any attempt to do so resulted in a recurrence of falling. She consulted her family physician who examined her, but could find nothing wrong. Three months later, in June, 1939, she lost control of her bowels and bladder. There was, however, a gradual return of these two functions. She began to have a feeling of "drawing up" of her arms along with some difficulty in walking. No pain or paresthesias were present. She was afraid to try to walk alone for fear she would fall.

Physical examination on admission revealed a well-nourished and well-developed Negro female whose only complaint was that mentioned above. A neurological examination revealed good muscular power throughout; there was a bilateral ankle clonus and Babinski; hyperactive knee jerks and ankle jerks; reflexes of upper extremities were good; loss of muscle tone and sense in lower extremities associated with a coarse intention tremor; abdominal reflexes not obtained; no nystagmus or scanning speech; gait was spastic, uncertain, and jerky, and she walked with a broad base. Laboratory work as follows: hemoglobin, 70 per cent; red blood cells, 3,900,000; white blood cells, 6500; serologic test for syphilis was negative; spinal tap, negative. She was observed in the hospital for ten days and was discharged in the same condition as on admission, and with a diagnosis of multiple sclerosis.

The patient was seen in the obstetric clinic on Sept. 14, 1945, for the first time. At this time, she was seven weeks pregnant, blood pressure was 132/88, weight was 110 pounds, and was apparently in satisfactory condition. She had had a full-term child in 1933, the prenatal course being complicated by a mild case of pre-eclampsia. On Feb. 15, 1946, the patient was admitted to the hospital for a check on her condition. At this time, examination revealed pupils which were unequal, and there was a suggestion of unsustained nystagmus of both eyes. There was moderate weakness of all muscle groups of her legs which was associated with a bilateral sustained ankle clonus—the latter more pronounced on the left. Abdominal reflexes were absent; Babinski, positive, bilateral; Rhomberg, strongly positive; and the heel to knee test was done very poorly. Her gait was ataxic. It was the opinion of the medical consultant that her condition was not any worse than when she was seen in 1940.

After an essentially normal prenatal course, and after fourteen hours of labor, she delivered a full-term child weighing 6 pounds 3¼ ounces by low forceps following central episiotomy. Her labor and puerperium were normal, and there was no exacerbation of her multiple sclerosis. Sterilization was recommended following delivery, which was refused.

This patient was seen one year following delivery. She stated: "The only thing I notice is a tendency to drag my left leg a little which was not noticeable before." Otherwise, her condition was quite satisfactory. There have been no subsequent pregnancies.

CASE 3.—E. C. This patient, a 30-year-old white para 3-0-0-3 was admitted to the hospital on June 7, 1943, because of multiple sclerosis, and with the strong recommendation of the referring physician that pregnancy be interrupted. Her past obstetric history is interesting, and is presented in detail for it brings out the reason why she was admitted.

Her first pregnancy was in 1931. She delivered a full-term living child which was normal in all respects following an uneventful prenatal course. Three months following delivery, she developed a sudden complete blindness of her right eye. This lasted three to four days, but gradually cleared up. There were no other signs or symptoms. Her second pregnancy in 1933 was uneventful so far as her prenatal course, labor, and puerperium were concerned. However, one month following delivery, she developed a painful nearly complete blindness of her left eye. This blindness continued for about five days, with a gradual abating of the condition. Her third pregnancy in 1936 was uneventful and, again, there was the onset of pain with associated blindness of her right eye. This slowly cleared, but the patient remained below "par" physically and began complaining of numbness of her legs. In 1942, the patient had a recurrence of left eye blindness which lasted for one week. This was followed by weakness and numbness of both legs. She was hospitalized for four weeks because she was unable to walk without falling, and was handicapped by the unilateral blindness. While in the hospital, she was treated with vitamin B complex with little relief of pain or symptoms. At this time, a diagnosis of multiple sclerosis was made.

She was again admitted to the hospital on June 7, 1943, ambulatory, eight weeks pregnant, and for a therapeutic abortion and sterilization. Physical examination revealed weakness of the muscle groups of the lower extremities; no ataxia, no nystagmus, and all reflexes normal save for the absence of the abdominals and a positive Babinski of both feet. No eye studies were done. The pregnancy was interrupted by an abdominal hysterotomy followed by sterilization by the Pomeroy method. Postoperative course was uneventful, and she was discharged after thirteen days' hospitalization in satisfactory condition.

This patient has not been seen since her discharge from the hospital, and further information about her condition is not available.

CASE 4.—A. O. This patient, a 31-year-old white para 0-0-1-0 was admitted to the hospital on May 28, 1946, with a history of multiple sclerosis of some twelve years' duration. She was admitted for study and treatment. She was in her sixth week of pregnancy; her last menstrual period had been April 11, 1946, and her estimated date of confinement was Jan. 18, 1947. In February, 1934, she noticed that she was beginning to drag her left foot when walking. The condition became progressively worse, and in May, 1934, while out walking, she fell to the ground, got up, and fell again. She was unable to stand on her feet without falling. She lost confidence in herself and didn't make an attempt to walk for fear she would lose her balance and fall. She was treated from 1934 to 1937 by "needles" and, in 1937, began taking sodium thiosulfate intravenously. She continued to lose ground, lost the feeling in her left leg, and the leg became numb. She continued treatment with sodium thiosulfate until 1938 with little improvement in her signs and symptoms, so finally discontinued the drug. The only sickness was scarlet fever in childhood without complications. The patient was admitted to a hospital in 1941 for a therapeutic abortion because of her condition. Otherwise, the obstetric history was negative. The previous pregnancy didn't seem to aggravate her multiple sclerosis.

Physical examination on admission revealed an unsustained lateral nystagmus of the left eye. There was marked spasticity of the lower extremities with diminished muscular power. Also, there was a moderate amount of intention tremor. All the reflexes were increased and hyperactive, abdominals were absent, there was a loss of vibratory sense in the lower extremities, marked ataxia, and marked spasticity of the lower extremities. She could not walk without assistance. Laboratory findings were essentially negative, and the serologic test for syphilis was also negative. She was discharged after one week's

hospitalization, the decision having been made to allow her to continue with her pregnancy in that it was felt that the condition wouldn't be aggravated. However, one month later, the patient sought other medical advice and, without consulting us, was again hospitalized and aborted. The patient refused sterilization.

CASE 5.—T. I. This patient, a 24-year-old white para 1-0-0-1, was first seen in the hospital April 25, 1946. The first symptom, loss of vision following an attack of German measles, had its onset in February, 1945. She sought medical attention and was given a complete systemic checkup. Notation was made that the patient was quite unaware that she was dragging her right leg or that she was unsteady on her feet. She only complained of her left eye. Examination of the eyes revealed definite optic atrophy, a slow nystagmus on looking to either side, but more on looking toward the left. Neurological examination revealed a moderate Rhomberg response. The patient was awkward on her feet with eyes open. Pronation-supination test was poorly done with the arms. Deep reflexes were overactive in arms and legs, more marked on the right than the left, bilateral Hoffman reflexes, and a right Babinski. Laboratory work was essentially normal. Spinal tap revealed a Pandy of 3 plus; a colloidal mastic test of 4-4-3-2-2-1-0-0-0-0 which was stated as being highly suspicious of multiple sclerosis.

On admission to the hospital, she was in her first trimester of pregnancy—her last menstrual period had been Jan. 28, 1946, and estimated date of confinement, Nov. 5, 1946. The duration of pregnancy was approximately twelve weeks. The patient was admitted for study and treatment. There was no appreciable change in her condition since last seen. Her reflexes were as they were previously, and her ataxic condition was the same. She was discharged after fourteen days' hospitalization, with the decision to allow her pregnancy to continue.

Her first child, a full-term living baby born in 1941 without complications, was normal and healthy.

Her prenatal course was uneventful. There was no aggravation of her condition, and her pregnancy progressed uneventfully to term. She was delivered by central episiotomy and low forceps of a full-term living child weighing 6 pounds 8 ounces after three hours and forty-eight minutes of relatively mild labor—mostly back pains—on Nov. 7, 1946. Twenty-four hours post partum, she was taken to the operating room, where a routine Pomeroy sterilization was performed. Both the delivery and sterilization were done under spinal anesthesia. The Department of Neurosurgery was consulted, and they advised us there was no contraindication to using it in this case.

The patient has been seen on several occasions since delivery; she was last seen on Feb. 12, 1947. There has been no apparent exacerbation of her condition, and it can be said that her multiple sclerosis was not aggravated by her pregnancy.

Discussion

Above are the fairly complete records of five patients suffering from multiple sclerosis in whom the disease was complicated by pregnancy. Having studied these cases, what conclusion can be drawn? Are we any closer to an answer to Peckham's two questions as to the effect of pregnancy upon this disease and of the disease upon pregnancy, labor, and the puerperium?

These cases extend over a period of seven years from 1939 to 1946, and were treated by various physicians, although, more or less under the same general supervision.

Of the five, one, Case 3, was interrupted in our own clinic, and one, Case 4, elsewhere, although we felt that it should not have been done. Unfortunately, we do not have any recent information on the first of these two cases, and cannot say what her condition is at present. When she was first seen in 1939, our views on multiple sclerosis and pregnancy were still somewhat dependent upon those of the internist and neurologist, and it was more or less upon the recommendation of the consultants in these fields that the decision was made to interrupt the pregnancy. In the light of the present knowledge and belief of medical men and obstetricians, it is possible that pregnancy would have been allowed to continue in this case, although she did have a very bad history.

The other three cases would seem to warrant the conclusion, if we can draw one from such a small number of cases, that pregnancy has little, if any, effect on multiple sclerosis. The disease is one which is progressive and one in which remissions and exacerbations normally occur. It does not appear that the progress is accelerated by pregnancy, nor is pregnancy likely to cause exacerbations.

In these three cases, pregnancy proceeded more or less normally; there were no major obstetric complications, and labor was without special incident. All these infants were born alive and in good condition and did well. The puerperium was normal and uneventful.

From this, we can conclude that multiple sclerosis has no ill-effects upon pregnancy or upon offspring. It is our feeling at present that multiple sclerosis is not an indication for therapeutic abortion. There may be exceptions to this in individual cases where the disease is particularly severe. On the other hand, any woman afflicted with a condition as serious and as hopeless as multiple sclerosis appears to be at present, is probably better off if she is not burdered with a home and a family. The advice to remain single is good advice. If this is disregarded, perhaps contraceptives of one kind or another should be prescribed. Sterilization is only one method of carrying out contraception.

DYSGERMINOMA OF THE OVARY*

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D. S. HOSPITAL No. 186422. A female, aged 26 years, was first seen on Jan. 1, 1947, complaining of pain in right lower quadrant of four days' duration. The pain started while bowling. The past history was irrelevant. Menses started at the age of 12 years, were of the twenty-eight-day type, with a four-day flow. Her last period was Dec. 24, 1946. She had been married four years and there were no pregnancies, despite normal sexual relationships.

Examination revealed a well-developed white female about 120 pounds in weight. Her blood pressure was 120/80. The heart, lungs, head, and neck were normal. There was a slight bulging of the lower abdomen with a palpable, irregular mass occupying the entire left lower quadrant. Vaginal examination showed normal external genitals and a firm introitus. The cervix was small and pointed posteriorly. A hard, irregular, fixed mass involved the entire left adnexa and extended to the left anterior superior spine. The uterus was not palpable, although a line of cleavage could be ascertained between the body of the uterus and the adnexal mass. The right adnexa showed a tender palpable ovary.

On Jan. 14, 1947, under spinal anesthesia, operation was performed through midline suprapubic incision. A moderate amount of clear fluid was found in the peritoneal cavity. The left adnexa was found to be the seat of a large, irregular, nodular solid mass. The uterus was small. The right ovary was enlarged and cystic, with its attached Fallopian tube kinked. A supravaginal hysterectomy and bilateral salpingo-oöphorectomy was done. The patient made an uneventful recovery.

The specimen received in the laboratory was a uterus measuring 4 by 4 cm. in size removed supracervically with both tubes and ovaries attached. The serosal surface of the uterus was smooth and pink. The myometrium measured 2 cm. in thickness. The endometrium was pale and smooth. One tube measured 11 cm. in length and showed no gross pathology. The attached ovary measured 4 by 2 cm. in size, and on section revealed a 1 cm. lutein cyst and several smaller cysts. The other tube measured 4 cm. in length and showed no gross pathology. Its attached ovary measured 14 by 11 cm. The external surface was pinkish-yellow and was studded with numerous nodules of varying size. The capsule was apparently intact. On section a small amount of slightly turbid serosanguineous fluid escaped. Most of the ovary was firm, yellowish-white, and homogeneous. There were several irregular cystic areas interspersed, and the tissue was soft and hemorrhagic in the vicinity of the cysts. The nodules on the surface of the ovary were apparently due mainly to the lobulation of the mass. However, there were several nodules which were bright yellow in color and well demarcated from the remainder of the tumor (Fig. 1).

*Presented, in part, at a meeting of The Bronx Hospital Clinical Society on Mar. 3, 1947. Read at a meeting of The Bronx Gynecological and Obstetrical Society, Mar. 24, 1947.

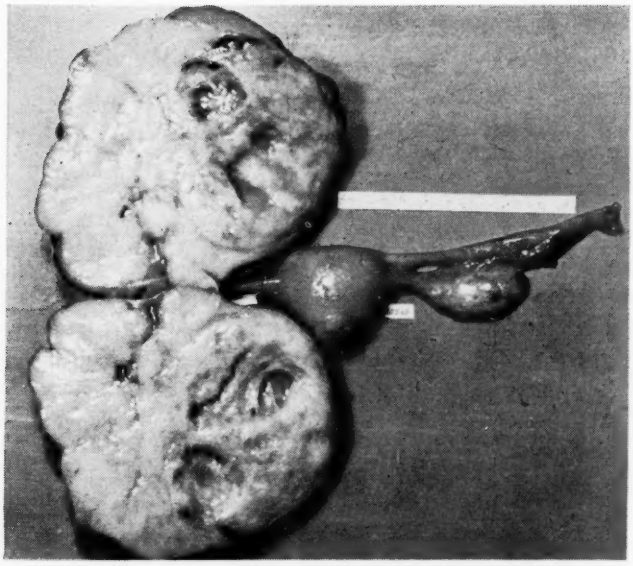

Fig. 1.—Operative specimen. (See text.)

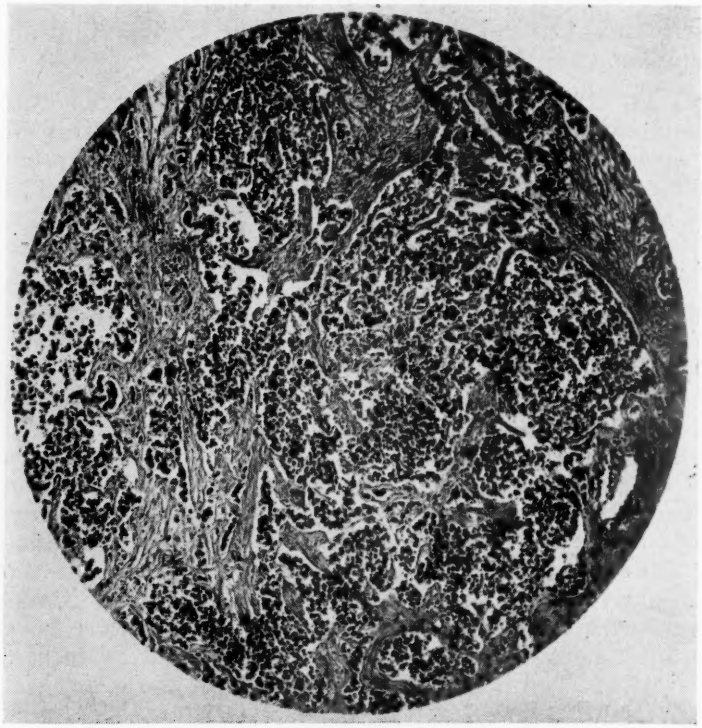

Fig. 2.—(×100.) Photomicrograph shows clusters of round or ovoid cells arranged in alveoli and separated by a hyalinized connective tissue stroma which is infiltrated with an occasional lymphocyte.

Microscopically, sections of the uterine wall showed the glands to be fairly normal in size, shape, and distribution. They were in the follicular phase with a compact stroma. Sections of the ovary revealed clusters of round or ovoid cells with clear, acidophilic, sparse cytoplasm arranged in alveoli and separated by a hyalinized connective tissue stroma. There were large areas of necrosis present. Section of the other ovary revealed several follicle cysts, one of which was filled with acidophilic secretion. Several corpora albicantes were present. Sections of Fallopian tubes showed no essential pathologic changes (Fig. 2).

Diagnosis.—Dysgerminoma of the ovary.

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PAROTITIS COMPLICATING THE EARLY PUERPERIUM

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THIS case is reported because of the rarity of its occurrence.[1-4] In the last ten years, among more than 26,000 deliveries at The Bronx Hospital, there occurred only one case of parotitis complicating the puerperium and one case of parotitis associated with pregnancy. The latter was a three and one-half months' spontaneous abortion in which swelling of the right parotid developed three days following passage of the products of conception. This was diagnosed as of the epidemic variety.

R. H., No. 186744, a 26-year-old gravida ii, para i, stated that she never had "mumps." However, following her first delivery on Sept. 15, 1944, on the eighth postpartum day, she developed swellings in front of both ears which lasted several days. This was not accompanied by temperature elevation.

In this delivery, the prenatal course was complicated by a slight but persistent albuminuria. The blood pressure was always low, varying only between 98/50 to 92/60. At no time did the patient exhibit edema or an excessive gain in weight; she was 151 pounds on Jan. 16, 1947. The Kahn and Wassermann reactions taken Oct. 17, 1946, were both negative, and the Rh factor was positive. Dental examination revealed caries of the upper and lower third right molars and the lower left third molar.

On Jan. 20, 1947, the patient was delivered of a living 7 pound 6 ounce male baby spontaneously, following a ten-hour labor. There was a first degree laceration which was repaired. The placenta and membranes were delivered and were complete and intact following a five-minute third stage.

During the first five postpartum days, the patient's temperature did not rise above 98.6° F. On the evening of the sixth day, the temperature rose to 101.6° F. Examination at this time showed that the pharynx was reddened, and glands were felt at the angles of both jaws. Except for these findings, the physical examination was negative.

On the following day, the temperature reached 103° F., with a slight acceleration of the pulse to 102. There could now be noted diffuse enlargement of both parotids. They had a rubbery hard consistency, but were only slightly tender. Each gland extended from the preauricular region to the angle of the jaw. The pharynx was clear. There was slight pouting of the opening of Stenson's duct, but no marked redness existed. The patient had very few subjective symptoms, and did not exhibit any discomfort upon chewing and swallowing foods, including even the very sour fruits.

Examination of the blood on the seventh day post partum at the height of the swelling showed 4,120,000 red blood cells, with 11.9 Gm. hemoglobin, 4,700 white blood cells, with a differential count of 69 per cent neutrophiles, 14 per cent band forms, and 17 per cent lymphocytes.

On January 28, the eighth day post partum, the temperature reached 100.6° F. The left parotid gland had begun to decrease in size. The white-cell count on this day was 6,000, with 55 per cent neutrophiles, 16 per cent band forms, and 29 per cent lymphocytes.

On the following day, the temperature was 99.6° F. The right submaxillary gland was now palpable and enlarged. However, the lymph glands were no longer palpable.

On January 30, the patient was seen by a diagnostician from the Department of Health, and the clinical diagnosis of parotitis was concurred, but the type was not definitely interpreted. It was advised, however, that isolation which had been practiced should be continued.

X-ray films taken of the parotid areas on January 31 showed no evidence of calcification. Serum amylase determination on the same date showed an increase to 83 mg./100 c.c. over the normal of 20 to 40 mg./100 c.c. No agglutinins were found in the heterophile antibody titer determination.

A specimen of the patient's blood was sent to the Department of Bacteriology and Immunology of Harvard Medical School, and they reported a complement fixation test with mumps antigen and the patient's serum. The titer of the serum for mumps was very low, being 1:32, which was interpreted as indicating the possibility of mumps infection in the past. Another serum specimen drawn February 24, fixed complement in the presence of mumps antigen to a titer of 1:512. This would seem to favor the existence of a recent infection with mumps.

By the thirteenth day post partum, all the glands had completely subsided, and the patient was discharged the following day.

Comment

The question arises whether this patient had mumps or was suffering from a nonspecific parotitis. In this case, there is no history of exposure to the epidemic type. The rapid disappearance of the glandular swellings, the absence of lymphocytosis, the relative absence of tenderness,[5] and the history of similar glandular swellings during the previous puerperium all point to the nonspecific variety of parotitis even though the titer of one of the serum specimens in the complement fixation test with mumps antigen was high.

As regards the cause of nonspecific infections of the parotid glands, there are two generally accepted theories. One is the "pyemic" theory or the hematogenous infection and the other is the "ascending" or infection passing through Stenson's duct from the mouth.[6] The method of infection in this case could not definitely be determined, but the absence of any pyemic manifestation and the presence of defective mouth hygiene and caries of the molar teeth probably with associated deep-seated dental infection must be considered as probable etiological factors for the salivary glandular enlargements.[7]

The treatment of this case avoided the use of specifics such as the sulfonamides or antibiotics and included merely symptomatic therapy and the improvement of the oral hygiene. No surgical intervention was necessary in view of the absence of fluctuation and the rapid disappearance of the glands.

Summary

1. A case of parotitis whose onset began in the early puerperium is presented.

2. The history is unusual in that parotid glandular swellings occurred at the same stage of puerperium during the patient's both pregnancies.

3. Evidence is presented which would indicate that the infection is nonspecific.

Acknowledgment is hereby given for the advice and cooperation of Dr. Meyer Rosensohn and the staffs of the Department of Obstetrics and the Department of Pathology.

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PAPILLOMA OF THE CERVIX UTERI IN PREGNANCY

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IN 1945, Edmonson, Levi, Evans, and Horn[4] called attention to the occurrence of a rare squamous epithelial lesion on the cervix uteri in pregnancy. They described six instances of papillomatous proliferations of the cervix in pregnant women ranging in age from 17 to 22 years. The histologic changes seen in these lesions were divided into three groups: "(a) simple thickening of the epithelium; (b) greatly thickened, irregular epithelial units indiscriminately fused together with confluent tiny papillary stalks; (c) large papillomatous growths."

In reviewing the literature, Edmonson, Levi, Evans, and Horn[4] found several references to the lesion under discussion. Cullen[2] and Norris[9] stated that condyloma may occur on the cervix in pregnancy. Mershon[6] reported two cases of papilloma in patients both aged 22 years, and in the sixth week of pregnancy.* DeLee[3] mentioned in his text that he had seen three instances of nodular hypertrophy of the cervix in pregnancy.

Besides those cited by Edmonson and associates, we have discovered in the literature several other cases of papillomatous proliferation of the cervix in pregnancy. Meyer[7] reported two specimens, one of which he described as a pointed condyloma, and the other as a circumscribed papilloma in a 27-year-old woman who miscarried at four months. Mohnle[8] recorded in detail a papilloma of the cervix in a 31-year-old multipara who had a miscarriage during the fourth month of gestation. Treite[10] added two cases, one a pointed condyloma found in a 27-year-old woman pregnant for nine months, and the other a circumscribed flat papilloma in an 18-year-old primigravida in the third month of pregnancy.

Because of the infrequency of reports of papillomatous lesions of the cervix uteri in pregnancy, we describe an additional case.

Case Report

CASE 1.—E. S., an 18-year-old Negro primipara, was first seen in the prenatal clinic of the Edward J. Meyer Memorial Hospital on June 19, 1946. Date of the last menstrual period was April 24, 1946. Expected date of confinement was Jan. 31, 1947. The patient had a scant leucorrhea. The prenatal record mentioned that the patient showed no evidence of gonorrheal infection. The Wassermann test taken on the first visit was reported as negative.

The patient was admitted to the hospital on Feb. 2, 1947, in active labor. Examination revealed a left occipitoanterior position. The blood pressure was 150/100. Urinalysis showed one plus albumin and one plus sugar, with negative findings in the sediment. The patient was delivered of an 8 pound 12 ounce male infant by episiotomy and low forceps. Duration of the labor was thirteen hours and forty-five minutes.

Immediately after the delivery of the fetus the cervix was pulled down and inspected. It appeared normal except for an area on the anterior lip. Here was seen a circular, white, edematous papule estimated about 1 cm. in diameter,

*One of these cases was included in the report of Edmonson et al.

with multiple, minute, short papillary projections on the surface. The entire lesion was excised following the application of a suture ligature about the base, and submitted for pathologic examination to exclude malignant tumor.

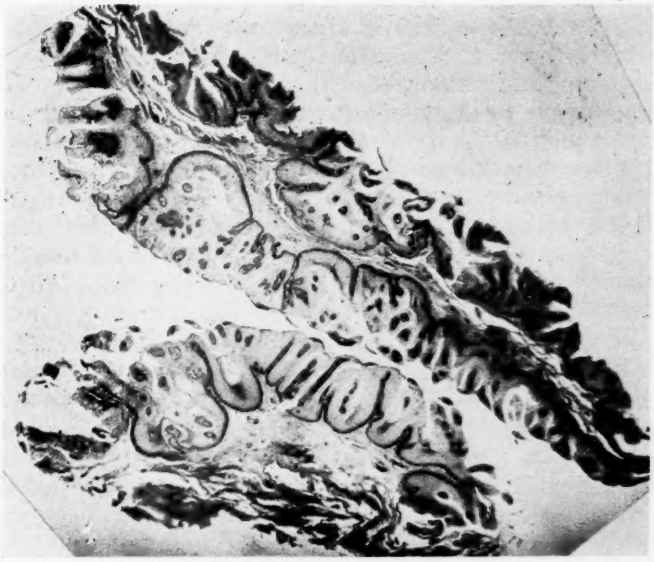

Fig. 1.—Low power view of the entire papilloma.

Fig. 2.—Epithelial appearance of the papilloma.

Pathologic Report.—Grossly, the biopsy specimen measured 2.5 by 1.2 by 0.4 cm. Microscopic examination of the cervical lesion revealed a papillomatous growth, with multiple, branching processes, covered by a distinctly thickened stratified squamous epithelium. The basement membrane was intact. The basal cells were large, with large nuclei, and appeared fairly uniform. Mitotic

figures of the normal type were frequent. In some areas the superficial layers of the epithelium showed a slight to moderate focal infiltration of neutrophiles. The superficial cells showed marked vacuolization. Parakeratosis was present in some areas and keratinization was minimal. In a few areas the stratified epithelial proliferation was related to the columnar cells of the underlying glands. The central stalk of the papillary processes was composed of a highly vascular connective tissue stroma. The small blood vessels and capillaries were distinctly hyperemic, and hemorrhage throughout the stroma was a prominent feature. There was slight edema, with infiltration of round cells, plasma cells, and a few neutrophiles. A few cervical glands were present, one of which showed slight cystic dilatation. No decidual cells were noted. The diagnosis was squamous papilloma.

The patient's course following delivery was uneventful. She was discharged from the hospital on Feb. 13, 1947. Her last blood pressure was 128/82; urinalysis showed a negative albumin, two plus sugar, and 10 to 15 pus cells per high power field.

The patient was last seen at the postnatal clinic on March 14, 1947. Examination of the cervix revealed a parous external os. The anterior lip showed a small nodule, about 0.3 cm. in diameter and elevated about 0.2 cm., which was not in the same location as the original lesion. The nodule was excised, and in addition, biopsies were taken from the anterior and posterior cervical lips. Smears and cultures of the urethra and cervix did not show gonococci. Complement fixation test for gonorrheal infection was reported as negative.

Pathologic Report.—Microscopic examination of the small nodule on the anterior lip of the cervix showed slight inflammation, chiefly superficial, with infiltration of neutrophiles and round cells, and edema. Hemosiderosis was present. No stratified epithelium was found in the specimen.

The small biopsy fragment of the anterior lip of the cervix, taken from the base of the previously removed papilloma, revealed injection of capillaries, edema, and slight infiltration of neutrophiles, round cells, and plasma cells. The preserved epithelium, which was of the stratified and columnar type, was crushed. No invasion could be seen.

The biopsy from the posterior lip revealed slight inflammation with hemosiderosis. It was covered by columnar epithelium.

Discussion

That papillomatous lesions of the cervix under any circumstance are of rare occurrence is evident from the relatively few reports in the literature.[4, 6, 7, 8, 10, 11]

In addition to its rarity, the papillomatous lesion in our case was of interest because of its association with pregnancy, and because of its gross appearance which stimulated the clinical impression of a possible malignant tumor. In our abstract of the literature, we have already referred to the occurrence of papillomatous lesions of various grades in pregnancy.[4] There is still discussion on the etiologic and pathogenetic factors for these lesions. Meyer[7] stated that pregnancy may play some part in the cause other than contributing an increased susceptibility to inflammation. Edmonson and associates[4] suggested the hormones associated with pregnancy were determining factors. Hofbauer,[5] who demonstrated proliferative changes in the cervical mucosa and glands during various stages of pregnancy, also mentioned hyperplasia of the portio epithelium. It was his belief that the anterior pituitary hormone might be responsible for both of these cervical changes.

Papilloma of the cervix has occasionally been reported in nonpregnant women, apparently on the basis of inflammation. Gonorrhea appears to be the

commonest offender, although tuberculosis is also a frequent cause. Other factors included are chronic discharge and mechanical stimuli from a pessary. Norris[9] held that condylomas of the cervix in pregnancy were secondary to gonorrheal cervicitis. In our case, however, the clinical, bacteriologic, and histologic findings offer no convincing proof for an infectious cause.

The lesion in our case fell into the group of large papilloma, and the lesion, because of its gross appearance, raised the clinical suspicion of a malignant growth; histologically, though in active proliferation, it showed a benign character. It is interesting to note that several patients with papillomatous lesions of the cervix were treated with radium therapy, apparently on the suspicion of malignant tumor from the gross appearance,[4] and that certain papillomatous lesions were originally considered malignant by pathologists after microscopic examination, later to be regarded as benign, only after review of the slides.[7] Cattaneo[1] went so far as to write: "Papillomas of the portio, besides being rare, very rarely are benign in as much as often they are the precursor of a malignant epithelial tumor." He further added that they should be regarded in the same manner as polyps of the rectum and papillomas of the urinary bladder. On the other hand, Meyer,[7] who classified papillomatous lesions into three types: (a) pointed condyloma, (b) flat diffuse papillary growths, and (c) circumscribed papilloma, stated that there was no evidence for considering the possibility of a malignant transformation in these lesions.

Summary

1. The literature on papilloma of the cervix uteri in pregnancy is briefly reviewed.

2. An additional case of papilloma of the cervix in pregnancy is reported in detail.

3. Papilloma of the cervix can be separated into two main groups: (a) inflammatory, (b) gestational. The etiology of each is briefly discussed.

4. The points of view on malignant transformation are presented.

The authors wish to express their thanks to Dr. Samuel Sanes for his kind assistance in the preparation of this article.

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A MODIFIED METHOD OF SURGICAL REPAIR FOR PROLAPSE OF CERVICAL STUMP WITH ASSOCIATED ENTEROCELE

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THE prolapse of a cervical stump following supravaginal hysterectomy is a distressing occurrence following abdominal removal of a uterus. The surgical repair is difficult in that attempts at repair per vaginum often are attended with partial or complete closure of the vagina, or, if the vagina is maintained as a functioning structure, the repair is often incomplete.

There have been many methods of repair advocated, ranging from removal of the cervix and ligamentous apposition and closure to fixation of the cervix to the pubis.

In the case herewith reported the patient was a 61-year-old multiparous white woman. Twelve years ago an abdominal supravaginal hysterectomy was performed at another hospital. About one year ago she noted a bulging in the vagina which became progressively worse. There was an associated frequency and some dysuria. Examination revealed an elderly woman in good general condition. Vaginal examination disclosed a large cystocele and prolapse of a cervix, with a small external os completely outside the vagina. Palpation revealed the cervix almost entirely absent, with only a vaginal cuff of cervix remaining. Posterior to the cervix was an enterocele about the size of a lime. There was a small rectocele. The patient was admitted to the hospital and operation subsequently performed.

Operation.—Under spinal anesthesia, an inverted T incision was made just above the external os and carried up to the urethra. The vaginal mucosa and its underlying fascia were bluntly dissected off the bladder and superiorly and laterally to the pubis, revealing the subpubic fascia. The bladder was then stripped off the remnants of cervix, which proved to be about one-half inch long, until the peritoneum was visible. The cross arm of the inverted T incision was extended posteriorly, completing the denudation of the cervical cuff. The cervix was then divided anteriorly, through the external os in a longitudinal direction up to the peritoneum. At the top of this incision, the cervix was split by a transverse incision through the anterior lip. The cervical cuff was thus transformed from a small cylinder to a flat rectangle. Since in this case there was no secreting endocervix, no denudation was necessary. If the endocervix is functioning, it should be removed. This flap was then sutured by interrupted white cotton sutures to the subpubic fascia, after the bladder had been pushed back into the pelvis above the pubis. The posterior vaginal mucosa which had been incised and freed from the cervix was then dissected further posteriorly. The uterosacral ligaments were palpable and sutured together without opening the peritoneum of the posterior cul-de-sac, and then sutured to the superior margin of the transposed cervical flap. The anterior vaginal flaps, which had not been trimmed off, were divested of the outer layer of mucosa by shaving a thin layer off with a scalpel. This shaving extended upward almost to the lateral edges of the pubis. The flaps were then divided so as to obtain two strips of tissue (one on the left and one on the right), about three-fourths inch wide, maintaining its integrity above. The right strip was then crossed over the transplanted cervical flap and sutured to the subpubic fascia. The same procedure

was then used, carrying the left strip to the right subpubic fascia. Thus was constructed crossed layers of denuded mucosa and fascia sutured to the subpubic fascia, in the fashion of sliding grafts, creating a sling under the transposed cervical flap. The excess vaginal mucosa was trimmed off and sutured together from below the urethra down to the point where the top of the plication of the uterosacral ligaments had been started. The posterior vaginal mucosa was then trimmed and sutured to the bottom edges of the anterior layer. A high perineal repair was then completed in the usual manner. Upon completion, the reconstructed vaginal tube admitted two fingers and extended about three inches in depth. A retention catheter was placed in the bladder and the patient returned to bed in good condition.

The postoperative convalescence was uneventful, and the patient was discharged home on the thirteenth postoperative day. Examination on discharge revealed a well-healed perineum. The vagina admitted two fingers. The anterior vaginal wall was healed, and there was no bulge on straining. A thick ridge could be felt under the symphysis pubis, and the vaginal canal was patent for about three inches. There was no bulging or relaxation at the dome of the vagina. Re-examination, six months later, revealed no change.

Summary

A typical case of prolapsed cervical stump with associated enterocele and cystocele following abdominal supravaginal hysterectomy is described. A modified method of repair utilizing sliding fascial-mucosal grafts and transposition of cervical flap is described.

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Special Article

CURRENT TEACHING TRENDS IN OBSTETRICS*

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THE first course in midwifery in the American colonies was given by Dr. William Shippen in Philadelphia in 1762. He, John Morgan, and Thomas Bond established the first medical school in the colonies in 1765 in Philadelphia under the auspices of the University of Pennsylvania.

It has taken the past fifty years to eliminate the diploma mills and unapproved schools. There is one still surviving in the United States.

The need to be approved by the Council on Medical Education and Hospitals for internships and residencies of the American Medical Association and the continuing surveys by the American Medical Association and the American College of Surgeons, has resulted in vast improvement in the quality of service rendered and instruction given in our hospitals. Credit is also due to the Association of American Medical Colleges. This is the framework in which young men and women have been and are being prepared for the practice of medicine and, more particularly, obstetrics. The ingredients for producing the kind of physician who can best serve the public are threefold: the caliber of the teachers, the quality of the students, and the availability of adequate teaching facilities at all levels of medical education.

The final factor in education is the teacher. This is the ingredient which will in the main determine the quality of our physicians. The objective of the real teacher must be to arouse and maintain interest, to stimulate independent thinking, to help develop powers of observation.

There are three types of research:—clinical; basic; that is, investigations in the allied sciences which have a clinical bearing; and abstract. Most well-run hospitals afford opportunities for clinical research. University hospitals, in addition, can support basic research in conjunction with the departments of the allied sciences. Abstract research has no place in a medical environment. Teachers certainly should have an understanding of the implications and potentialities of clinical and basic research.

I am firmly convinced that heads of medical school departments in our specialty certainly, and probably in all clinical specialties, should be seasoned clinicians who have a flair for teaching and an appreciation of research. Students, interns, residents, and junior members of the department are entitled to that kind of leadership.

The part-time professorship seems to be an ideal compromise between the full-time professorship and the clinical professorship. This is the most widely

*From the opening address before the American Congress on Obstetrics and Gynecology, September 8, 1947, St. Louis, Mo.

favored plan at the present time. From the standpoint of the school it is more economical than the full-time professorship. It is less restrictive and more broadening in opportunities for the individual and generally more inviting to any capable man than either of the others. Under this plan, men may be attracted to come to a school from elsewhere if that is desired, or local men find it possible to discontinue the routine and relatively minor parts of their private work in order to give more time to the school.

In recent years the magic word "research" has become a shibboleth in medical schools and hospitals. Many, including trustees of schools and hospitals, have begun to regard it as the touchstone of qualification. Nothing could be further from the needs of the junior physicians and the women for whom they are to render care.

Research in all its ramifications is the foundation of progress. Laboratory research is primarily the province of the younger physicians who have the imagination and the leisure and should get their leads from their elders. Clinical research can be carried on throughout a lifetime clinical career.

Good teachers have certain characteristics. They enjoy teaching. They have the gift of stimulating and holding the interest of their students, and they have a broad personal knowledge of that which they are teaching.

In recent years some well-established schools and some new state medical schools, handicapped by limited resources and perhaps blinded by the radiance of the magic word "research," have selected department heads who still had their spurs to win on the battlefield of clinical practice. I believe this is an unkindness to such men and a gross injustice to their students, interns, residents, and staffs. Never forget that our keenest critics are those whom we undertake to teach.

However, the financial needs of the faculties of most of our medical schools, the teachers who must train the physicians of the future to care for the entire population in health and disease, continue to be neglected. Very few schools have an income and budget which enable them to compete for medical teachers against the lure of private practice. State university medical schools are steadily assuming a greater role in the training of physicians at all levels of development.

There are 70 approved medical schools in the United States. They have a combined active teaching faculty of 1,516. There are also 292 well-organized hospital maternity divisions with approved residencies. The department heads and chiefs in the obstetric divisions of these schools and hospitals do not change overnight. There are currently 2,395 Diplomates of the American Board of Obstetrics and Gynecology and, in addition, approximately 4,800 mature and well-qualified clinicians who have not seen fit to seek Board Certification. Surely, out of these two groups replacements can be found which will meet with general approval on the basis of experience and teaching ability.

Organized medicine, state medical societies, and school alumni associations should take on as one of their most urgent tasks a campaign to increase these state school budgets sufficiently to enable them to pay adequate salaries to de-

partment heads, or to include the privilege of private practice. This will attract the kind of leaders such departments should have.

The junior teachers can well be of two kinds, those with a clinical background and those with an interest in or a capacity for basic research. Here, too, salaries should be sufficiently attractive plus practice privileges to hold the better men. Thus all grades of students will be exposed to a properly balanced faculty under real leadership.

I am particularly concerned with this trend away from seasoned leadership on behalf of the thousands of established physicians who are being urged to take advantage of refresher courses and postgraduate instruction. Surely they have a right to expect that their teachers have been exposed to the problems which have confronted them.

I believe I have justified the thesis that the quality of leadership in our teaching institutions is of prime importance. The essential qualification among these leaders must always be adequate clinical experience for which there is no substitute.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

This **Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears**[1] by Gates and Warren appears in a very attractive form. Papanicolaou has written the foreword. It has been published with the help of the Massachusetts Division of the American Cancer Society. The technique is described in great detail. The main value of the book lies in its fifty beautiful plates covering every aspect of findings, including the normal ones. The text is short, and is really a commentary and elucidation of the plates.

No matter what one's opinion may be, this type of diagnostic investigation has come to stay. Even if some of its advocates and introducers are too sanguine, the method certainly has value.

When I see the data of Papanicolaou and Traut, of 7,000 to 10,000 smears with the percentage error of 0.3 per cent, only twelve false negatives and no false positives, I must express my doubts, because I have had several cases of positive smears taken by men who have had full experience in the technique, where subsequent curettage and biopsy as well as observation have shown that there was no neoplasm. R. T. FRANK.

Practical Office Gynecology by Karnaky[2] is a very personal book containing a great deal of information and also a great many personal interpretations, some of which certainly will require revision. The purpose of the book is to describe the symptoms which may be elicited in the office and particularly treated medically, probably a revulsion against the "overzealous exercise of surgical judgment" which in plain English I interpret as "unnecessary surgery." The author emphasizes that uterine bleeding is controlled by changing the blood level of estrogens. This he does by means of diethylstilbestrol. He places great faith on diagnosis of the acid reaction in the vagina, ovulation determinations for sterility, particularly by the rectal temperature changes, and the endometrial biopsy method. The author is a great believer of the uses of stilbestrol which seems to be his cure for almost all the gynecologic ills to which women are subject. Of 3,982 patients given stilbestrol, 82 per cent experienced nausea and vomiting no matter whether the drug was prescribed parenterally or

[1] **A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears.** By Olive Gates, M.D., Pathologist, Massachusetts State Tumor Diagnosis Service; Assistant Pathologist, Pondville Hospital (Massachusetts Department of Public Health); and Shields Warren, M.D., Assistant Professor of Pathology, Harvard Medical School; Pathologist, New England Deaconess and New England Baptist Hospitals; Reserve Consultant in Pathology to the Bureau of Medicine and Surgery, United States Navy, Captain (M.C.) U. S. N. R. With a foreword by George N. Papanicolaou, M.D., Ph.D., Associate Professor, Department of Anatomy; Research Associate, Department of Obstetrics and Gynecology, Cornell University Medical College and New York Hospital. 182 pages. Harvard University Press, Cambridge, Mass. 1947.

[2] **Practical Office Gynecology.** By Karl John Karnaky, M.D., Assistant Professor of Clinical Gynecology, Baylor University College of Medicine; Gynecologist to Jefferson Davis Hospital, Houston, Texas; Director of Menstrual Disorder Clinic, Jefferson Davis Hospital; on Courtesy Staff of St. Joseph Infirmary, Memorial Hospital, Hermann Hospital, Heights Hospital, Park View Hospital and Methodist Hospital, Houston, Texas. 261 pages. Charles C Thomas, Springfield, Ill. 1947.

orally, but he is convinced that if they kept on, this nausea always disappears. He controls bleeding by means of 5 mg. of stilbestrol, by mouth, every fifteen minutes. In severe cases, he injects an oily solution of stilbestrol directly into the cervical tissue. According to Karnaky, 100 mg. of stilbestrol, taken in from 3 to 6 weeks, reduces polycystic ovaries to normal. Before hysterectomy he gives from 250 to 1,000 milligrams. In 4,134 endometrial biopsy specimens he found secretory endometrium in only 5 per cent of all women who suffer from excessive bleeding. These biopsies are done on the first day of the menses. In women under 35 years old, or where carcinoma is not suspected, he does office curettages for menorrhagia. After having performed 1,557 kymographic tracings, he believes that they are as accurate as endometrial biopsies for the determination of ovulation. However, as far as one can judge, he has no controls whatever to substantiate this assertion which in both tests rests more upon credulity than actual proof. Fifty consecutive patients have not aborted since stilbestrol was started, giving 10 mg. daily. When there is cramping or spotting, he gives 50 to 100 mg. every fifteen minutes. Another illustration of the author's heterodoxy is the fact that he considers the ordinary pregnancy test too time-consuming, and places much reliance on vaginal scrapings which, if they turn black with iodine, he considers a proof of pregnancy; also if 5, 10, or 25 mg. of stilbestrol do not cause vomiting or nausea, 90 per cent of these patients are pregnant; and finally, if the vaginal pH is between 3.5 to 3.9, it is further proof. I could continue giving instances covering the rest of the book, but this will give the reader a very good idea of what to expect. There is much that is stimulating, new and interesting, but a good deal of it has to be taken with several grains of salt.

The monograph is faultlessly presented, contains many good illustrations and a number of colored plates which to most readers will prove familiar, as they have been borrowed from the pharmaceutical advertisements with which physicians are showered. R. T. FRANK.

The second edition of Wharton's **Gynecology With a Section on Female Urology**[3] has appeared. The first 760 pages deal with gynecology. The succeeding 240 pages are devoted to urology. Both sections go into details of each specialty. One can consider the presentation as that current at the Johns Hopkins Hospital, and still influenced to some degree by the methods of the late Howard Kelly. The text is clear and to the point. The exposition is conservative, but takes in all of the newer acquirements. The book is beautifully illustrated, largely based on pictures culled from the literature, which in this case are chosen with such care and intelligence that they show more than any single author ordinarily could present if he limited himself to his own collection.

I would suggest that among the pessaries to be described the Gellhorn receive attention and illustration, and even the old Schatz has its value. An unusually good chapter on the sympathetic nervous system is worth-while reading. I note with pleasure that in urology the water cystoscope is finally described, although previously the Johns Hopkins gynecologists have remained faithful to the Kelly air cystoscopy, which in my opinion has a much more limited application. Altogether the book is very satisfactory. R. T. FRANK.

Functional Surgery in Gynecology[4] is a peculiar book. It covers the operative indications, the operative techniques, the physiological and physiologico-pathological aspects of endocrinology, on the whole, in a very satisfactory fashion. The strangeness of the book consists of the fact that it appears to have been written behind a Chinese wall. With the

[3] **Gynecology With a Section on Female Urology.** By Lawrence R. Wharton, Ph.B., M.D. Assistant Professor of Gynecology, The Johns Hopkins Medical School; Assistant Attending Gynecologist, The Johns Hopkins Hospital; Consultant in Gynecology, The Union Memorial Hospital, Hospital for the Women of Maryland, Sinai Hospital and Church Home and Infirmary. Second Edition. With 479 Illustrations. 1027 pages. W. B. Saunders Company, Philadelphia and London. 1947.

[4] **Chirurgie Fonctionnelle Gynécologique.** Indications opératoires, techniques et considérations pratiques en rapport avec les acquisitions endocrinologiques. R. Bourg, Chef du service universitaire de gynécologie a l'Hôpital Brugman, Bruxelles. Preface de E. Douay, Président de la Société Française de Gynécologie, Paris. 267 pages. Masson & Cie. Paris (VI[e]). 1947.

exception of five or six vague references to the literature, the only way of recognizing the fact that others have done work in gynecology is from the naming of a few operations with author's name such as the Alexander, the Pozzi, and the presacral resection of Leriche.

The author displays great faith in endometrial biopsy. He insists on the use of lipiodol in salpingographs and does not even mention the water soluble media. While the sulfonamides are mentioned, penicillin is not referred to. The book is well illustrated, contains a wealth of good material, and should be of great service particularly to the general surgeon who dabbles in gynecology and has not the time to keep abreast of the newer, particularly less radical procedures such as myomectomy, inplantation of the tubes, resection of the ovaries, ovarian grafts, etc. R. T. FRANK.

The 1946 Transactions of the American Society for the Study of Sterility[5] contains a large amount of interesting material with good discussions. This rather small but apparently very active society based its first discussion on Methods of Increasing Fertility in Domestic Animals by M. G. Fincher, D.V.M., from the Veterinarian College of Cornell University. I am glad to see that physicians are again paying attention to the excellent work done by veterinarians who are able to control the material in a fashion impossible in human beings. An article of considerable value is that by Halford of Honolulu, based on Observations on Racial Fertility and Sterility in Hawaii where Hawaiians, part-Hawaiians, Puerto Ricans, Caucasians, Chinese, Japanese, Koreans, and Filipinos have lived in harmony for many years. The Effect of Prolapse of the Ovaries Upon Cystic Degeneration and Ovulation by Weed and Collins is far from convincing. Greulich has carefully studied the Reliability of "Basal" Body Temperature Changes as an Index of Ovulation in Women. His well-controlled experiments are a very good indication of ovulation and conception but, as he says, there is no reason to believe that the technique is infallible. X-ray Irradiation to Promote Ovulation is discussed by Haman. Rommer's discussion of Psychoneurogenic Causes of Sterility and Their Treatment, With Preliminary Remarks on Allergenic Sterility discusses a new field but is far from being completely convincing, although the author believes that there are definite psychogenic and neurogenic causes for sterility which act through "a hormone-sympathetic imbalance in the system"; an interesting secondary observation were the definite vaginal and cervical contractions demonstrated by intracervical and intrauterine graphs connected with a kymograph system during coitus. A number of other articles are of great interest but cannot be reviewed in detail. R. T. FRANK.

A short monograph on **Leucorrhea in the Female**[6] covers the subject in a rather detailed fashion. Particular attention is paid to *Trichomonas vaginalis.* The world literature is taken up in detail. R. T. FRANK.

The twenty-first volume of the **Annales of the Obstetric and Gynecological Institute of Helsinki's University** appears under the editorship of Mauno Rauramo,[7] to whom the volume is dedicated. It also incldues the twenty-fifth volume, second supplement of *Acta Obstetricia et Gynecologica Scandinavica.* Fortunately for the reviewer, a great majority of the articles are written either in German, French, or English, or have summaries in these languages. The University Clinic sees close to 4,000 patients a year, in a ratio of 3 to 1, in obstetrics and gynecology. The first 100 pages are devoted to statistical tables. Then follow a large number of diverse articles covering both obstetrics and gynecology, some of

[5]**1946 Transactions of the American Society for the Study of Sterility.** Edited and published by The Western Journal of Surgery Publishing Company, Portland, Oregon. 174 pages.

[6]**Flujos Genitales Femeninos.** Dr. Alonso Restrepo. Trabajos de la Academia de Medicina de Medellin. Reproduccion de "Anales de la Academia de Medicina de Medellin"—III Epoca—Vol. III—No. 2—Julio, 1946.

[7]**Annales Instituti Obstetricii et Gynecologici Universitatis Helsinkiensis.** Edidit Mauno Rauramo. Tom. XXI, Anno MCMXLV.

them in reprint form, bound with the main volume. Of particular interest are corpus carcinoma in infants, three cases of primary tubal carcinoma, and two cases of cervico-uterine fistulae. R. T. FRANK.

Practical Obstetrics by Mayes[8] comes from the far anitpodes. The volume grew out of bulletins on obstetrics for wartime graduates in the services. Its main aim is to be practical, clinical, and is meant for young doctors going into practice. Its motto is "early diagnosis: late interference." The presentation is in the form of histories of actual cases as, for instance, in the beginning two cases of postpartum hemorrhage, a discussion of the forms of treatment to be considered, and then a description of these treatments, including manual removal of the placenta, the injection of pituitrin and ergot preparations, Crédé's extraction. Lovsett's technique of delivering the arm in breech presentations is advised. The manual rotations of occipitoposteriors is described, and if this is ineffectual, to pass the hand beyond the head, hooking the shoulders around. The description of forceps is limited to the axis traction instrument. Such procedures as episiotomy, lower segment cesarean, induction of labor, induction of therapeutic abortion, especially by hysterotomy, the treatment of sterility, artificial insemination are taken up; likewise a discussion of the Rh factor in pregnancy, rubella, and pregnancy. It is a well-designed book, profusely and well illustrated by drawings by Schiavo, and contains a number of colored plates in addition. The book should serve its purpose very well, particularly in isolated communities where the doctor is left entirely on his own. R. T. FRANK.

Will and Agüero have published a handsome fascicle which they call **Obstetric Illustrations,**[9] for the reason that they hope to continue these publications, and secondly that although the context is variegated and far from complete from many points of view, it represents the special cases culled from a large obstetric clinic where 6,000 patients are confined each year (Concepción Palacios). The text is very short, hardly more than explanatory to the beautiful, large sized lithographs (6½ by 8½ inches). They cover everything from a normal full-term uterus, with and after the fetus has been removed; rupture of the uterus; abdominal pregnancies; and then a number of unusual fetal deformities, gross and in gross section. This beginning of an atlas should prove of use, particularly where a large clinic material is not available. It is the first publication from Venezuela that we have had for a long time, and is therefore welcome because it shows that this part of South America is taking part in the wonderful strides in advancing medicine that South America is now showing. R. T. FRANK.

Miscellaneous

Female Sex Endocrinology by Calatroni, Ruiz, and Di Paola[10] is a large, profusely illustrated, and minutely documented monograph covering the subject in an unusually

[8]**Practical Obstetrics.** By Bruce T. Mayes, M.V.O., M.B., B.S. (Sydney), F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G.; Professor of Obstetrics, University of Sydney; Senior Honorary Obstetrician, King George V. Memorial Hospital for Mothers and Babies, Sydney; Honorary Obstetrician, Royal Hospital for Women, Sydney; Honorary Consulting Obstetrician, Women's Hospital, Crown Street, Sydney. Drawings by Vergil Lo Schiavo, B.A. (Sydney), Diploma Royal Academy (Rome and Florence). 306 pages. The Australasian Publishing Co. Pty. Ltd. Sydney. 1947.

[9]**Ilustraciones Obstetricas.** Por los Doctores Gerardo Will, Ex-adjunto del Instituto de Anatomía Patológica (Director: M. Ascanazy) de la Universidad de Ginebra.—Médico Anatomo-Patólogo de la Casa Municipal de Maternidad "Concepción Palacios," Caracas.—Investigador en la Facultad de Medicina e Instructor de la cátedra de Histología Normal de la Universidad Central de Venezuela y Oscar Agüero, Médico-Partero, Adjunto del Servicio No. 2 de la Casa Municipal de Maternidad "Concepción Palacios," Caracas. Prologo Par el Doctor: Leopoldo Aguerrevere, Profesor de Clínica Obstétrica de la Universidad Central de Venezuela. Casa Municipal de Maternidad "Concepción Palacios," Caracas. 1946. Editorial Grafolit, Caracas, Venezuela, 1947.

[10]**Endocrinologia Sexual Femenina.** Carlos J. Calatroni, Docente libre de Clinica Ginecológica (Buenos Aires); Vincente Ruiz, Ex prof. titular de C. Ginecológica (La Plata) Jefe del Serv. de Ginecología del H. Español (Buenos Aires); Guillermo Di Paola, Docente libre de Clínica Ginecológica (Buenos Aires) Subjefe de Servicio del Hospital Rivadavia. Prólogo del profesor Dr. Bernardo A. Houssay. 724 pages. Libreria Y Editorial "El Ateneo," Buenos Aires. 1947.

objective, sober, and carefully worked-out fashion. Its format, many colored illustrations, and minute chapter bibliographies are rarely found in these days of paper shortage. The literature, particularly the American literature, has been utilized to a great degree, but in such a fashion as to not interfere with smooth reading.

The main subjects dealt with are embryology, anatomy, and physiology of the female; the separate endocrine glands; and finally, the female sex hormones. Childhood and adolescence, and maturity and senility are taken up in turn. The menstrual cycle is divided into uniphasic (anovular); biphasic (follicular and corpus luteum phase); and triphasic which constitutes pregnancy. In the description of glands, the treatment is equally thorough and consecutive. Under the chapter on thyroid, the authors have not as yet included thiouricil and its derivatives. The chemistry of the estrogens and progesterone is taken up in great detail. Among the endocrine glands, the authors justly place the chorio-placental system which is so often treated in a stepchild fashion. At the end there is a miscellaneous agglomeration of aphorisms which are both amusing and instructive. For example, they mention that the relation between the spermatozoan and the entire volume of man is 1:1,000,000,000.

This volume fills a definite gap in the Spanish literature. It should serve to keep the Spanish reading readers fully informed both of the newest knowledge in female sex endocrinology, as well as the world's literature, in a very pleasant, readable volume.

R. T. FRANK.

Cameron's **Recent Advances in Endocrinology,**[11] which is one of the Blakiston **Recent Advances Series,** has its sixth edition after an interval of only two years. This compact small volume is replete with information, and has gradually assumed a useful balance between investigative and laboratory versus clinical data so that today it has become a useful book for reference, particularly for those who are not able to keep up fully with the literature. In this connection it would be well if the index were made more detailed and if an index of authors were added.

The new edition coming so soon after the previous one shows comparatively little changes among the few new acquirements. The production of artificial iodo-proteins and the employment of thiouracil should be mentioned. Each short chapter bibliography has been brought right up to date.

As I have previously mentioned, these **Recent Advances Series** occupy a position between the so-called yearbooks and more detailed treatises. They have a distinct advantage over the yearbooks in that continuity is kept up so that the full subject is dealt with. Cameron, who is professor of biochemistry, Medical Faculty of the University of Manitoba, is in intimate contact not only with the English but also with the American literature, which is of advantage to the reader.

R. T. FRANK.

A 540-page compendium on "**The Endogenous Endocrinotherapy Including the Causal Cure of Cancer**" from the pen of Jules Samuel of Amsterdam[12] has been published. To my mind this would show that the credulity of people in Europe is about on a par with that found in the Western Hemisphere. This large volume is a continuation of the publications of this author which have appeared since 1936. It is to precede the publication by this same author of five volumes giving the complete and extensive description. The entire method is based on a spectroscopic examination of the blood, which is supposed to show various deficiencies and ailments at a preclinical stage. This book is written in English.

R. T. FRANK.

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[11]**Recent Advances in Endocrinology.** By A. T. Cameron, C.M.G., M.A., D.Sc. (Edin.), F.R.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Sixth Edition. 443 pages. With 74 figures, including Three Color Plates. The Blakiston Company, Philadelphia and Toronto. 1947.

[12]**Endogenous Endocrinotherapy including the Causal Cure of Cancer.** Compendium. By Dr. Jules Samuels. Specialist for endogeneous endocrinotherapy. Amsterdam. 540 pages. Holdert & Co., Amsterdam. 1947.

Hormonal Aspects of Procreation[13] is merely a part of his more ambitious publication just reviewed. The main theme is the assertion that the activator of the ovum is the gonadotropic hormone absorbed from the hypophysis. R. T. FRANK.

The first monograph from Vienna since the war that has come into our hands is that by Dr. Gottfried Hartmann, who describes a very rare case which he calls **Osteophthisis of the Pelvis and Femur.**[14] This female patient was watched for many years in the clinics of Vienna. The pelvic girdle became a soft tissue, as did the upper portion of the femur. She was twice delivered by cesarean section and finally died, permitting a full autopsy. Some aspects of the case were not studied, such as the blood chemistry, which after all would have been of supreme importance. The author, after giving the full history and autopsy reports of the patient, then reviews the various bone conditions which should be taken under consideration in diagnosis, including bone atrophies, aseptic necrosis, inflammatory conditions, parasites, Hand-Schüller-Christian disease, primary and metastatic bone neoplasms. The monograph is illustrated with a number of x-ray pictures of the patient's bones.

R. T. FRANK.

The first edition of **Diseases of Metabolism,** edited by Garfield G. Duncan, was reviewed in 1942. It then already appeared to be a standard book of reference. This opinion is confirmed by the second edition,[15] which has just appeared. Six new contributors and practically all of the old ones have written the text. The volume has increased by some 60 pages. As a matter of interest, the first introduction was written by Frederick Banting. The foreword to this second edition is by Charles H. Best. As heretofore, understanding, diagnosis and treatment of the various metabolic disorders are discussed. Two new chapters have been added, one on the thyroid and its diseases; the other, on disorders of the kidney.

During the five years which have elapsed, understanding of the role of proteins in wound healing, in the development of immunity, and in controlling the rate of convalescence, has greatly increased. Some advances in knowledge of nutrition and its deficiencies has taken place. In the present volume, the importance of folic acid has been noted. Alloxan diabetes is described. As heretofore, no attempt to include endocrinology as a whole has been made but wherever endocrine disturbances affect metabolism, this has been incorporated. The new edition has considerably increased the value of this important guide and certainly has brought it up to date. R. T. FRANK.

Excerpta Medica[16] is a new monthly review of the world literature dealing with radiology. This is Volume I, No. I, Section 14 of this undertaking. The active editors

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[13]**Die Hormonalen Aspekte des Fortpflanzungsprozesses.** von Dr. Jules Samuels, Chirurg-Frauenarzt, Spezialarzt für endogene Endokrinotherapie. 152 pages. Holdert & Co. N. V., Amsterdam, Holland. 1946.

[14]**Osteophthisis Pelvis et Femorum.** Zugleich ein Beitrag zur Frage der Spontanen Rückbildung Maligner Tumoren. von Dr. Gottfried Hartmann, Assistent Des Pathol. Anat. Institutes der Universität Wien. Mit 19 Abbildungen. Wiener Beiträge zur Pathologie und Pathologischen Anatomie. Bd. 1. 183 pages. Wilhelm Maudrich, Wien, 1947. Distributors in U. S. A., Grune & Stratton, Inc., New York.

[15]**Diseases of Metabolism.** Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner. Edited by Garfield G. Duncan, M.D., Director of Medical Division, Pennsylvania Hospital; Clinical Professor of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania. With Contributions by Walter Bauer, Hugh R. Butt, Abraham Cantarow, Tracy Donald Cuttle, Garfield George Duncan, Frank Alexander Evans, Ferdinand Fetter, Joseph Marchant Hayman, Jr., Martha A. Hunscher, Friedrich Klemperer, Cyril Norman Hugh Long, Perry MacNeal, Edward H. Mason, Max Miller, Louis H. Newburgh, John Punnell Peters, W. D. Robinson, Tom D. Spies, Leandro Maués Tocantins, Abraham White, Alexander W. Winkler. Second Edition, Illustrated. 1045 pages. W. B. Saunders Co., Philadelphia. 1947.

[16]**Radiology being Section XIV of Excerpta Medica.** A complete monthly abstracting service of the world medical literature comprising fifteen sections and covering the whole field of theoretical and clinical medicine. Under the general editorship of M. W. Woerdeman, M.D., F.R.N.A.S., Professor of Anatomy and Embryology in the University of Amsterdam, Chairman, A. P. H. A. De Kleyn, M.D., F.R.N.A.S., Professor of Oto-, Rhino-, Laryngology in the University of Amsterdam, W. P. C. Zeeman, M.D., Professor of Ophthalmology in the University of Amsterdam. Vol. I, No. 1, Section XIV, June, 1947. N. V. Excerpta Medica, Amsterdam C. (The Netherlands).

are all from Amsterdam, while the Board covers the entire globe. The object is to incorporate every article on radiology appearing in the medical literature of the world. Some will be included by title only, the more important to be in the form of informative abstracts, but condensed so as to be easily read. Each contribution will bear the signature of the specialist who has prepared it. The review is to go back to 1940 in order that the articles which appeared during the war and the articles that were frequently inaccessible may be included. Not only is general radiology, but radiological diagnosis of each of the body systems, and finally radiotherapeutics are included. R. T. FRANK.

It seems a far cry from gynecology and obstetrics to **The Foot and Ankle, Their Injuries, Diseases, Deformities and Disabilities** by Lewin.[17] However, if for no other reason, a short chapter on *The Relationship of Foot and Ankle Conditions to Urology, Gynecology, and Obstetrics* would warrant this review if any apologies were necessary. This thoroughly revised edition incorporates within its pages the vast knowledge gained through World War II. This includes the use of chemotherapy as a prophylactic and curative agent, the free use of plasma, etc. In the new edition there has been a revision particularly on compound fractures crushing wounds, osteomyelitis, and ringworm, both as a primary and secondary condition. The main object of the book is to act as a guide for medical officers of the armed forces. To show how the specialties have become aware of general medicine, there are interesting discussions of psychosomatic problems; neurological lesions; deficiency, metabolic and glandular diseases; dermatological affections and particularly changes of interest to the gynecologist and obstetrician. The relation of back, pelvis, hip, thigh, knee, to the foot and ankle. R. T. FRANK.

Boyd's **Surgical Pathology**[18] has a sixth edition after an interval of five years. This popular and standard textbook has always aimed to give the surgeon an insight into live pathology. It had this aim and hope long before the American Board emphasized this branch of medicine and insisted that the surgical specialist have this training.

In the present edition the pathology and pathologic physiology of the heart diseases has been given new chapters because of the rise of surgical interest in these conditions. Among the new material are included tumors of the larynx, pinealoma, Bittner's milk factor in relation to breast carcinoma, avitaminosis in cancer of the mouth, the Papanicolaou vaginal smear method in the diagnosis of carcinoma of the cervix, fibrous dysplasia of bone, inflammatory nodules of muscle in chronic arthritis, and fibrositis of the back. The book, as previously, is well written has 530 illustrations, and chapter bibliographies. R. T. FRANK.

Massons has written a monograph which is an Introduction to the **Study of Intravenous Therapy.**[19] It is a concise, well-written description covering every phase of intravenous

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[17]**The Foot and Ankle. Their Injuries, Diseases, Deformities and Disabilities.** By Philip Lewin, M.D., F.A.C.S., Associate professor of Bone and Joint Surgery, and Acting Head of Department, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital; Attending Orthopaedic Surgeon, Cook County Hospital; Senior Attending Orthopaedic Surgeon, Michael Reese Hospital, Consulting Orthopaedic Surgeon, Municipal Contagious Disease Hospital, Chicago; Formerly Colonel, Medical Corps, Army of United States. With 389 Illustrations. Line Drawings by Harold Laufman, M.D., F.A.C.S., Associate in Surgery, Northwestern University Medical School; formerly Major, Medical Corps, Army of the United States. Third Edition, thoroughly revised. 847 pages. Lea & Febiger, Philadelphia. 1947.

[18]**Surgical Pathology.** By William Boyd, M.D., Dipl. Psychiat., M.R.C.P. Edin., F.R.C.P. Lond., LL.D. Sask., M.D. Oslo, F.R.S.C. Professor of Pathology, The University of Toronto. 6th edition. With 530 Illustrations including 22 color figures. 858 pages. W. B. Saunders Company, Philadelphia and London. 1947.

[19]**Introducción al Estudio de la Plasmoterapia.** par José M. Massons. De la Sección de Farmacología del Instituto de Investigaciones Médicas de la Universidad de Barcelona (Fundación de la Excma. Diputación). Prólogo de Francisco García-Valdecasa. Catedrático de Farmacología de la Facultad Médica de Barcelona. 276 pages. Miguel Servet, Barcelona. 1947.

therapy including blood plasma, transfusion, and the various blood substitutes. Technical details are fully entered into. There is a copious bibliography. This monograph should be valuable to the Spanish-speaking readers. R. T. FRANK.

Feminine Psychology[20] is an ecstatic and dramatized depiction of the art of attracting, conquering, and conserving love. Its appeal is not to a medical circle of readers.
R. T. FRANK.

[20]**Psicología Femenina.** Arte de Atraer, Conquistar Y Conservar el Amor. By Maria J. Obregon de Marin. Imprenta La Milagrosa, Habana. 1944.

Correspondence

Management of Placenta Previa

To the Editor:

In his report on "The conservative management of some varieties of placenta previa" (American Journal of Obstetrics and Gynecology 50: 248, 1945), H. W. Johnson states: "In conclusion may I, for statistical purposes, make the following request? Will you please report to me any fatal case of placenta previa which you may know about, where there had been no cervical nor intrauterine manipulation, nor any attempt at manual removal of remaining placentae tissue during the third stage of labor. . . . This offer has been made many times during the last fifteen years, and at many of the 'refresher courses' offered by the State of Texas several years ago. These courses were attended by many of the older practitioners. I have, as yet, no case with which to start the series. Certainly, somewhere, sometime, someone must have died from placenta previa without having received energetic or heroic treatment."

A case meeting Dr. Johnson's "requirements" has come to my attention. I am reporting it, not so much with the view of having the distinction of starting Dr. Johnson's series, but rather because the case has general points of interest worth recording.

S. L., a 34-year-old white woman, was admitted to the Crown Heights Hospital, Brooklyn, on June 25, 1946, at 12:30 A.M. complaining of severe abdominal distress, worse on breathing. The patient was a gravida ii, para i. She had a child, 4 years old. Her last menstrual period was Sept. 20, 1945; the expected date of delivery was June 27, 1946. The prenatal course was uneventful except for an episode of slight vaginal bleeding about four weeks prior to admission. The patient was instructed at that time to rest in bed and report any further bleeding to her attending physician. On the night of admission, the patient felt well, ate a hearty meal, and was sitting outdoors with her neighbors. At midnight she began to feel abdominal pains and discomfort, which became rapidly worse. She was rushed to the hospital. Upon admission examination by the house resident revealed a short, stout woman, acutely ill, cyanotic, with labored breathing. Her temperature was 104.4; pulse 130; respirations 35. Heart sounds were normal. Lungs were clear; no râles were audible; no dullness on percussion. Abdominal examination revealed a full-term uterus which was hard and tender. Fetal heart was heard over the left lower quadrant, 140 per minute, of good quality. Rectal examination showed the cervix high and soft. The dilatation could not be definitely ascertained. Fifteen minutes after admission, while the patient was being shaved, she had a profuse hemorrhage from the vagina. The bedclothes were thoroughly soaked with blood. A few minutes later, the patient had an involuntary bowel movement.

The patient was seen by me about one-half hour after the bleeding episode. She was in complete shock, restless, tossing in bed, and gasping for breath. Her skin was cold and clammy. Her pulse was imperceptible at the wrist. Her blood pressure was unobtainable. The uterus felt hard and contracted. The fetal heart sounds were inaudible. There was no active vaginal bleeding at that time. The patient was given ¼ grain of morphine sulfate. Blood plasma was administered intravenously. Blood typing and RH factor determinations were ordered. The patient failed to respond to the medication and plasma injection, and expired about twenty minutes later.

An autopsy was performed and the positive findings were as follows: Congestion and edema of the lungs. The uterus contained a full-term male fetus in the left occipitoanterior position. The placenta was lying in the lower pole of the uterine cavity, completely covering

the internal cervical os. The cervical canal was filled with fresh blood clots. The external os was soft, admitting the tip of the index finger. The diagnosis was central placenta previa with hemorrhage.

In an attempt to retrace the symptomatology and course of this unusual case, one may draw the following conclusion: this was apparently a case of central placenta previa at term with, at first, a concealed retroplacental hemorrhage. This was responsible for the severe abdominal pain, general distress, and rise in temperature. Later, external hemorrhage occurred throwing the patient into irreversible shock. followed by death.

In summary a case of central placenta previa with profuse hemorrhage, followed by death, is reported. Except for one rectal examination, the patient had no vaginal examination or any other manipulations. Autopsy showed the only pathology to be that of central placenta previa with evidence of hemorrhage. The congestion and edema of the lungs were probably secondary.

SIMON BRODY, M.D.

842 EASTERN PARKWAY
BROOKLYN, N. Y.
OCTOBER 6, 1947.

Nutritional Deficiency and Menstrual Disturbances

To the Editor:

In the October, 1946, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY (page 611) R. R. Greene and B. M. Peckham presented a "critical review" of our work on the relation of nutritional impairment of hepatic function to menorrhagia and other endocrine disturbances. By coincidence, the October issue of the *Journal of Dental Medicine* carried a quotation from William James which is so apt that I requote it here:

"There are three stages in the history of every medical discovery. When it is first announced, people say it is not true. Then, a little later, when its truth can no longer be denied, they say it is not important. After that, if its importance becomes sufficiently obvious, they say, 'Anyhow, it is not new.' "

The critique by Greene and Peckham, when viewed chronologically in relation to the three basic elements of this problem, is in remarkable accord with William James' analysis. Thus, that the healthy liver inactivates estrogen is now considered by them to be so well established, it is no longer new. That the livers of animals deficient in vitamin B complex cannot inactivate estrogen is also admitted to be true, but they say, the effect is due solely to the accompanying inanition, so it is unimportant. And, as for the etiologic relation of nutritional deficiency to menstrual disturbances, this is so fantastic, they say frankly, we don't believe it.

But Greene and Peckham were not content with permitting the subject to rest, so far as they are concerned, in the realm of opinion. They have contrived a scathing condemnation of our clinical observations and have attempted to bolster their derogatory views with a variety of superficially plausible objections. Unfortunately, their objections are of necessity purely theoretical, since nowhere in their "review" is there any indication that either the authors (or the equally caustic discussant) investigated even a single human case to determine whether there is any correlation between the lesions of nutritional deficiency and the endocrine disturbances, or to find out whether the latter responds to nutritional therapy.

Apparently Greene and Peckham knew of only one clinical study on the subject other than ours, that of Ayre and Bauld, and they are much incensed at the fact that these workers obtained results in agreement with ours; this paper too is dismissed as too fantastic for credibility. But other studies on the subject were available at the time their paper was presented, had they troubled to search the literature. For it seems that whenever the subject has actually been *investigated* and not simply *dismissed,* results similar to ours have been obtained (P. M. Sosa and M. R. Monserrat: *Prensa Med. Argentina* **31**: 2657, 1944; H. Peters and W. Footer: *Permanente Found. Med. Bull.* **3**: 137, 1945; M. Hellman: *Prensa Med. Argentina* **32**: 1447, 1945).

Analysis of the arguments of Greene and Peckham reveals some curious twists of logic and actual mistatements of fact. Quotations from our articles are so presented as to give the impression that, for instance, a concise summary, or a statement that one phase of the work is still in progress, is somehow reprehensible. We are condemned for conducting nutritional studies in human beings on the basis of animal experiments, yet the basis for this condemnation is the animal experiments of Drill and Pfeiffer. The latter have claimed that the failure of inactivation of estrogen in the liver which we have reported in vitamin B complex deficiency (and which has been confirmed by numerous other workers) is due solely to the associated inanition and not to the vitamin deficiency. The discrepancies between the results obtained by Drill and Pfeiffer and the conclusions drawn from them by these authors, have been considered in detail elsewhere (*Vitamins & Hormones* **4**: 147, 1946) and need not be presented here. Greene and Peckham claim further that "Two of the early symptoms of vitamin B complex deficiency are anorexia and loss of weight," a statement that is simply in contravention of the facts. It is implied on this assumption that our patients could not have had nutritional deficiency, since the majority were of normal weight and many even of excess weight. The occurrence of lesions of vitamin B complex deficiency (e.g., atrophic glossitis, cheilosis, peripheral neuritis) in well-nourished persons is so well known as hardly to merit further discussion. The visible lesions in our patients have routinely been recorded by Kodachrome photography and many of the photographs of nutritional lesions, together with photomicrographs of the estrogenic endometriums of the same patients, have either been published or presented publicly; hence there need be little argument about the occurrence of either the nutritional or the endocrine lesions in our patients, or of their response to nutritional therapy.

The data demanded of us as the price of winning the credence of authors and discussant are truly fabulous. Intensive activity of the personnel of a well-staffed research institute could hardly supply all of it in the six and one-half years we have been working on the problem. Do the authors suggest withholding publication of our data simply because all its implications have not been investigated?

Further detailed discussion, point by point, of the questions raised by Greene and Peckham, would require an article at least as long as theirs, and almost all the issues raised by them have already been discussed at length elsewhere (*Vitamins & Hormones* **4**: 147-185, 1946; *Am. J. Clin. Path.* **16**: 737, 1946). But a few misconceptions, especially evident in the discussion, merit correction. First is the suggestion that the diets of our patients should have been analyzed or that vitamin excretion studies should have been done, conclusively to demonstrate nutritional deficiency. It is of course very well known that dietary deficiency per se (which was certainly common enough in our patients) is only one of a vast number of causes of nutritional deficiency.

Numerous studies have indicated that lesions of nutritional deficiency may be produced even in the presence of an adequate diet by factors which impair absorption of essential nutrients (e.g., gastrointestinal disturbances, biliary disease), or increase the requirement (e.g., pregnancy and lactation, hyperthyroidism, excessive physical activity, infections), or interfere with utilization (e.g., radiation therapy), or increase destruction (e.g., estrogens, sulfonamide drugs, industrial poisons) or excretion (e.g., lactation, excessive perspiration, polyuria). This subject has been reviewed by Norman Jolliffe (*Handbook of Nutrition*, Am. Med. Assoc., 1943, Chapter 24) and is summarized in a table in an article by Jolliffe and Most (*Vitamins and Hormones* **1**: 80, 1943). As for vitamin excretion studies, it is equally well known that these are of limited value as the tests reflect tissue levels very erratically. When patients have lesions of vitamin deficiency that can be detected with the naked eye (e.g., cheilosis, glossitis, gingivitis, skin lesions) or with a vibrometer (early peripheral neuritis) why surrender clinical acumen to dubious laboratory data?

Second is the suggestion that estrogen assays should have been performed on our patients. There is no question that such studies meticulously performed, have been of great value. But they are extremely laborious and time-consuming and often yield data of doubtful validity, owing to cumulative chemical losses and biologic variability. The latter frequently involves

errors up to 1,000 per cent, especially as the quantities of estrogen available from blood and urine are so small as to forbid the use of a sufficient number of animals. Improved technics may eventually make such methods more generally useful, but at present—analogous to the clinical versus laboratory diagnosis of nutritional deficiency—the patient's own endometrium seems at least as reliable an indicator of her endocrine status, as the tissues of a test animal.

MORTON S. BISKIND, M.D.

BETH ISRAEL HOSPITAL
NEW YORK 3, N. Y.
NOV. 8, 1947.

Replies by Drs. Greene, Peckham, and Huffman

To the Editor:

In writing the critical review we endeavored to be as objective as possible. Judging from the tone of Dr. Biskind's letter we did not succeed. We are sorry.

Dr. Biskind seems to imply that we are newcomers to this field and had no right to be critical. One of us, however, has long been interested in the subject of the effect of the liver on the metabolism of steroid hormones and has been a joint author with Dr. M. W. Burill of several publications on the subject (Proc. Soc. Exper. Biol. & Med. **44**: 273, 1940; Endocrinology **28**: 874, 1941; Endocrinology **31**: 73, 1942; Endocrinology **30**: 142, 1942). These had to do with the effect of the liver on testicular and adrenal steroids. They were not specifically concerned with the subject of the review and were therefore not mentioned.

Dr. Biskind considers us remiss in not thoroughly searching the literature. He quotes three articles in which he states results similar to his were obtained. The article by Peters and Footer appeared in the *Permanente Foundation Medical Bulletin* and was a general discussion article entitled *Gynecology in Industry.* Three paragraphs were devoted to the successful treatment of menorrhagia with vitamin B complex. No data were presented. We admit that we were remiss in not citing this article. We doubt, however, that under similar circumstances we would be able to find a similar article in a similar obscure publication with such a general title.

No search of the literature would have been necessary to find the articles by Hellman and by Sosa and Monserrat. They were well publicized in the November, 1946, issue of the Abbott Laboratories "What's New." Copies of this publication were sent to us and to every physician in the United States. One dealt with the treatment of mastalgia and dysmenorrhea with vitamin B complex and the other, the treatment of dysmenorrhea. The review had to do with B complex, menorrhagia, and cancer. These articles were, therefore, deliberately not included. Further comment does not seem necessary except to note that dysmenorrhea was not included by the Biskinds in the gynecologic conditions improved by B complex therapy.

Dr. Biskind has drawn inferences from our review that were not intended nor implied (fourth paragraph). We did not and do not believe that a concise summary is reprehensible; nor is a "statement that one phase of the work is still in progress." We condemned no one for conducting studies in human beings on the basis of animal experiments. We do believe, however, that the transfer of results obtained in the experimental animal to the human must be done with caution and with full realization of the possibility of species variations. This latter point may be very pertinent. An example may be found on some work published by Hooker, Drill and Pfeiffer (Proc. Soc. Exper. Biol. & Med. **65**: 192, 1947) subsequent to the presentation of our review but several months prior to Dr. Biskind's letter. In experiments similar to those performed in the rat by the Biskinds these workers have demonstrated that the liver of the monkey *(Macacus rhesus)* is not able to inactivate estrogens. In these animals (a species much closer to man than is the rodent) the addition of vitamin B complex did not enhance this nonexistant ability.

Space limitations prohibit further pursuit of this particular subject but we cannot resist pointing out several facts or theories ignored by the Biskinds in formulating the hypothetical rationale for their clinical use of vitamin B complex. The first is the known ability of the kidney to excrete estrogens in the free as well as the combined form. They ignore the possibility that the kidney could excrete this "noninactivated" estrogen theoretically present in vitamin B complex deficiency. Secondly they ignore the commonly accepted ideas as to the reciprocal relationships between gonad and hypophysial function. If an excess of estrogen did accumulate with vitamin B deficiency, in theory at least, it would depress the gonadotropic function of the hypophysis. The resulting depression of estrogen production should cause the estrogen level to return to normal and the same mechanism should maintain it at a normal level. This latter subject is admittedly theoretical in nature. However, one would logically expect the Biskinds to explain its nonvalidity rather than to consistently ignore it.

According to Dr. Biskind our statement that two of the early symptoms of vitamin B complex deficiency are anorexia and loss of weight, is "simply in contravention of the facts." We freely admit that this statement as written was partially erroneous. We wish to apologize for our carelessness. Only one article of three references on which this statement was based referred to vitamin B complex (Speis, T. D., Vilter, R. W., and Ashe, W. F.: J. A. M. A. **113**: 1931, 1939). The other two (Speis, T. D., Hightower, D. P., and Hubbard, L. H.: J. A. M. A. **115**: 292, 1940; and Foltz, E. E., Barborka, C. J., and Ivy, A. C.: Gastro-enterol. **2**: 323, 1944) referred specifically to thiamin chloride deficiency. In the last article only anorexia was noted since the subjects were on a fixed caloric intake.

Dr. Biskind states that "many of the photographs of nutritional lesions, together with photomicrographs of the estrogenic endometriums of the same patients, have either been published or presented publically." We have not been privileged to hear one of Dr. Biskind's public presentations. At the time the review was presented (Dec. 20, 1946) no photomicrographs had been published. Subsequently we have been able to find three photomicrographs published in *Vitamins and Hormones* (**4**: 147, 1946). (This book was received by the Chicago Medical Book Company on December 22, 1946, and was available in the Northwestern University Medical School Library on January 7, 1947.) These photomicrographs are labelled either "cystic hyperplasia" or "glandular cystic hyperplasia." As evidence of excessive and/or prolonged estrogen stimulation, the last two of the three are not convincing. As well as can be judged by the magnification used the second shows subnuclear vacuolization. This finding in the human being is accepted as evidence of early progesterone stimulation. The third photomicrograph is representative of the late proliferative stage and shows the edema of the stoma characteristic of this phase and not the crowded, closely packed stromal nuclei of hyperplasia.

The remainder of Dr. Biskind's letter in reality refers to Dr. Huffman's discussion and not to the review, and will be discussed by him.

We regret that Dr. Biskind has chosen to be so vigorously affronted by our review. Merely in the interest of accuracy may we remind him that his December, 1946, article was not published in the *Archives of Pathology* as stated in his letter but in the *American Journal of Clinical Pathology?*

R. R. Greene, M.D.
B. M. Peckham, M.D.

Northwestern University Medical School
Chicago, Dec. 5, 1947.

To the Editor:

Dr. Biskind's criticism of my discussion of the paper by Drs. Greene and Peckham has been read with great interest. I sincerely regret that Dr. Biskind has apparently taken personal affront at what were intended for objective comments. The primary object of the discussion was to point out what appeared, from a clinician's viewpoint, to be loopholes in the scientific proof of the hypothesis that vitamin B complex deficiency is capable of causing a

wide variety of gynecologic complaints and that it is of specific therapeutic value in these disorders. It is essential that any measures advocated for the prevention and/or treatment of a group of diseases including carcinoma of the uterus and functional metromenorrhagia be examined with thoroughness. This is particularly true when the advertising literature of major pharmaceutical manufacturers carries these therapeutic advances to the general medical public. Such criticism is not made with the thought of deriding the advocates. A scientific theory worthy of perpetuation and acceptance certainly should be able to withstand any criticism directed against it. If it cannot then it is not a valid theory.

I have had occasion to observe a considerable group of women suffering from functional uterine bleeding. These studies were not concerned with the patient's nutritional state. However, it was my impression that these patients did not present clinical evidences of gross vitamin deficiencies; a review of their case histories reaffirms that opinion. That patients with gross nutritional deficiencies may have genital disorders is not questioned. However, I do not believe that most patients with gynecologic complaints can be shown to have clinical evidence of vitamin depletion. If a subclinical deficiency is to be demonstrated it would appear that analysis of the diet to show a vitamin lack and excretion studies would be the logical way to do it.

Drs. Greene and Peckham have commented on the photomicrographs of endometrial hyperplasia which Dr. Biskind has used as evidence of hyperestrinism. I agree with their comments. It is true that errors do occur in estrogen determinations; it is also true that there may at times be some debate as to what constitutes endometrial hyperplasia. Also, many well-qualified gynecologists will question whether endometrial hyperplasia is always prima facie evidence of hyperestrinism.

I cannot accept Dr. Biskind's objection to the use of estrogen assays on the basis that they are extremely laborious and time consuming. Such difficulties, while perhaps slowing scientific efforts, should not stop them. It would surely not be too difficult to study a moderate-sized group of patients so that all critics would be satisfied.

I wish to reaffirm a statement previously made that I would welcome convincing evidence that a deficiency of Vitamin B complex is the cause and that its administration will cure these many gynecologic disorders.

J. W. HUFFMAN, M.D.

CHICAGO, ILL.
DEC. 5, 1947.

Leunbach's Paste

To the Editor:

In response to questionnaires to a large number of obstetricians and gynecologists concerning Leunbach's paste and similar preparations, the response was almost unbelievable in numbers and unanimity of opinion.

As a result of the information obtained from the questionnaires the Food and Drug Administration was able to embark on a campaign to rid the market of these murderous preparations. Our campaign was completely successful and resulted in removal of all such preparations from the market.

The originator of the business in this country, Adolph G. Schickert, was sentenced to a term in a Federal prison, and at the termination of his sentence was deported to Germany. Two other manufacturers served prison sentences, and the remaining two received heavy fines.

It would not have been possible to carry out this program without the wholehearted help and cooperation of a large number of obstetricians and gynecologists. Many of these very busy and public-spirited men left their practices to appear as witnesses for the Government in one or more of the trials which resulted from our regulatory efforts. Many other practicing obstetricians and gynecologists who were not called upon to testify for the Government gave their valuable time to answer our questionnaire and in advice and counsel. We would like to express our very deep appreciation to all of these physicians and to let them know that their efforts were not unavailing. It is not possible to communicate with each

one individually, so I am taking this opportunity to ask you if it would be possible to insert a notice in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY to inform these physicians who assisted us that the campaign was completely successful and to express our appreciation for their efforts.

We are fully aware that the highly lucrative returns from this type of business will tempt others to embark in this field. We have estimated that a tube of the preparation selling in the neighborhood of five dollars costs but a few cents to prepare for sale. We are, therefore, very much on the alert for the certain resurgence of this "racket," and you may be assured that when it appears the full resources of this Administration will be thrown into the battle to stamp it out.

G. A. GRANGER, M.D.
MEDICAL OFFICER.

FOOD AND DRUG ADMINISTRATION
WASHINGTON, D. C.
NOVEMBER 20, 1947.

Aspiration Curettage

To the Editor:

In the November, 1947, issue of the JOURNAL, Williams and Stewart, writing on aspiration curettage of the endometrium in a cancer clinic, refer to a report on office curettage by the undersigned. Williams and Stewart state: "They (Israel and Mazer) subject their patients to surgical dilatation and curettement without hospitalization. . . ."

May we take exception to the term, "surgical dilatation," which, to us, suggests a forceful act. The technique of office curettage described in the mentioned article does not include surgical dilatation. We state (AM. J. OBST. & GYNEC. 36: 445, September, 1938): "In multiparous women, the smallest (No. 1) Sims' sharp curette may then be passed without difficulty. However, in some nulliparous women, the cervical canal is narrow and requires preliminary dilatation. In such instances, the smallest metal dilator, moistened by a sterile water-soluble lubricant, is passed beyond the internal os. Following this, the curette readily enters the uterine cavity. . . ."

We do not regard surgical dilatation of the cervix as a feasible office procedure.

S. LEON ISRAEL, M.D.
CHARLES MAZER, M.D.

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DECEMBER 1, 1947.

Estrogens in Dysmenorrhea

To the Editor:

In the article of Doctors Torpin, Woodbury, and Child on "The Nature of Dysmenorrhea" (AM. J. OBST. & GYNEC., November, 1947), the authors erroneously credit Sturgis and Albright[1]) with the discovery that "large doses of estrogens administered early in the cycle abolished ovulation, and that the subsequent period was quite painless." The original report of Sturgis and Albright, however, refers to an earlier article by Dr. Raphael Kurzrok and myself,[2] acknowledges our prior use of estrogens in dysmenorrhea and confirms our observations regarding ovulation and corpus luteum function.

I first began to use estrogens in the treatment of dysmenorrhea in 1934. The prevailing theory at the time attributed the condition to excessive estrogen action resulting from absence or hypofunction of the corpus luteum. Quite by accident one of my patients was given estradiol benzoate, as a result of which she experienced the first painless period of her life. Further trials convinced me that this type of therapy was not without merit and I began an investigation into its *modus operandi.*

The method of estrogen therapy which I developed consists of two injections of estradiol benzoate in oil (1.66 mg. per dose) given intramuscularly one week apart during the first half of the menstrual cycle. It was first published in Doctor Kurzrok's[3] book (1937) and again in a paper in 1938.[2] It was in this paper that we first reported the significant, and now generally accepted, observation that functional dysmenorrhea occurs only in ovulatory cycles in the presence of a functioning corpus luteum. We attributed the absence of dysmenorrhea in anovulatory cycles to the absence of the luteal-phase contractions of large amplitude which normally appear after ovulation, and reach their maximum amplitude at the onset of the menses.

The desired goal of my method of estrogen therapy was to reduce luteal function (via anterior pituitary gonadotrophic inhibition) and thus restrict the development of the large contractions. When this result was attained (in approximately one-third of our cases), the ensuing period occurred several days prematurely, and generally was painless. With the same estrogen dosage, however, another third of the cases had periods which were delayed a few days to as much as four weeks (due to temporary suppression of ovulation); in the remaining third there was no alteration of the cycle. In both the prolonged and the normal-length cycles, the uterine contractions at the time of the flow were of the usual large amplitude. Nevertheless, in approximately 70 per cent of the cases, these periods were painless too, a result which I attribute to the psychic effect of suggestion. Sturgis and Albright's[1] modification of my method consisted of trebling the total estrogen dosage by giving a series of six injections at three-day intervals. By this means they completely suppressed ovulation and produced a painless estrogen-withdrawal bleeding.

While estrogen therapy has been of great value in helping to elucidate the nature of dysmenorrhea, and particularly in defining the somatic basis for the menstrual pain, I believe that it occupies a limited place as a practical method of therapy. It is true that there can be no dysmenorrhea without ovulation, corpus luteum function, and the large amplitude uterine contractions, but these are normal phenomena which are present in woman who ovulate and have no dysmenorrhea. There is little point in altering normal physiology to remove temporarily what is merely a symptom of a psychogenic disturbance. Psychotherapy is the direct approach and gives more effective, more lasting results.

LEO WILSON, M.D.

400 WEST END AVENUE
NEW YORK 24, N. Y.
Dec. 3, 1947.

References

1. Sturgis, S. H., and Albright, F.: Endocrinology **26**: 68, 1940.
2. Wilson, L., and Kurzrok, R.: Endocrinology **23**: 79, 1938.
3. Kurzrok, R.: The Endocrines in Obstetrics and Gynecology, Baltimore, 1937, Williams & Wilkins, p. 361.
4. Wilson, L., and Kurzrok, R.: Endocrinology **27**: 23, 1940.

Reply by Dr. Torpin

To the Editor:

Our sincere apologies are due to Dr. Wilson in failing to give him due credit for the first work upon this subject. This error crept into the paper, in spite of review study of more than 125 contributions to the literature of dysmenorrhea. Wilson and Kurzrok incidentally reported relief of dysmenorrhea in about 70 per cent of cases. Sturgis and Albright, undertaking to investigate the value of the method, used considerable care in dosage and timing, and were able to show that with attention to these details, the method, due to abolition of the ovulatory phase, was invariably effective in the next period but not during subsequent menses.

RICHARD TORPIN, M.D.

AUGUSTA, GA.
Dec. 20, 1947.